



JANUARY

# BULLETIN

OF THE NEW YORK  
ACADEMY OF MEDICINE



## *Original Articles*

*by*

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ACADEMY OF MEDICINE

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JANUARY 1940

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THE ADRENAL MEDULLA\*

W B CANNON

Professor of Physiology Harvard University

**A** FACT of fundamental importance in understanding the functioning of the adrenal medulla is its embryonic origin. Neuroblasts migrating outward from the primitive axis of spinal cord segments develop mainly into the ganglia of the sympathetic system, but some of them are transformed into the adrenal medulla. Thus most of these neuroblasts become sympathetic neurones, a small remnant become secreting cells which, on being stimulated, discharge adrenaline. Likewise, nearly all sympathetic neurones, when they are stimulated, discharge at their endings a substance which, according to strong presumptive evidence, has been regarded as adrenaline (Rosenblueth<sup>1</sup>, 1932). Since adrenaline is the characteristic constituent when extracts are made of the adrenal medullary cells and since sympathetic neurones are like the medullary cells in origin and in producing adrenaline, or an adrenaline-like substance, the question arose whether extracts of these neurones might not yield adrenaline.

The answer to that question was sought by Lissák and myself<sup>2</sup>

\* Presented October 27, 1939 at The New York Academy of Medicine in the Twelfth Graduate Tortnight

(1939) We found that extracts of the ultimate sympathetic fibers, the "adrenergic" fibers (e.g., those in the mesenteric nerves) or extracts of an organ containing such fibers (e.g., the heart) have all the effects of extracts of the adrenal medulla itself. They are like adrenaline in raising blood pressure, dilating the pupil, contracting the nictitating membrane, relaxing the non-pregnant cat uterus, augmenting the heart beat, and in other similar respects. Extracts of "cholinergic" nerves, and also extracts of the heart in which adrenergic fibers had degenerated, had no distinctive adrenaline-like action on blood pressure or iris.

The evidence strongly indicates, therefore, that Elliott's<sup>3</sup> (1904) suggestion is correct, that the ultimate sympathetic neurones influence glands and cardiac and smooth muscle by the adrenaline which they set free at their terminals, and that adrenaline secreted from the adrenal medulla and circulating in the blood stream has on these structures the same influence as the nerve impulses because it is the same substance as that which they produce. Since the sympathetic division of the autonomic system when strongly excited acts as a whole and thereby induces wide-spread changes in the organism—e.g., stopping the digestive processes, raising blood pressure, accelerating the heart, erecting hairs, as well as discharging adrenaline from the adrenal medulla—the combined, simultaneous action of sympathetic neuronal adrenaline and secreted medullary adrenaline is properly regarded as constituting a sympathico-adrenal system.

In addition to adrenaline discharged from the adrenal medulla, as a means of reinforcing or prolonging the effects of sympathetic nerve impulses, there is sympathin. This is a substance which escapes into the blood stream, from organs innervated by the sympathetic, when the sympathetic system is specially active. As we have noted, in these circumstances adrenaline is discharged from the nerve endings and has its typical effects. In doing so, however, some change occurs, because in some regions—in smooth muscles, for example—it causes relaxation and in others contraction. Rosenblueth and I<sup>4</sup> (1933), following a theory offered by Langley, have suggested that neuronal adrenaline unites inside the reacting cells with a differentiating substance which makes possible the two opposite responses to a single agent. In any case, sympathin differs from adrenaline. For example, ergotovine blocks the hypertensive action of adrenaline on blood pressure and reveals a depressive action, it has not that influence on the action of sympathin.

And whereas adrenaline retracts the iris and relaxes the cat's non-pregnant uterus, sympathin does not do so if it comes from a region where sympathetic nerves have a purely positive influence. In general, however, the positively acting sympathin prevails, causing, for example, acceleration of the heart and rise of blood pressure. The observations which Rosenblueth and I<sup>5</sup> made in 1932, and which later were extended by Liu<sup>6</sup> (1935), proved that secreted adrenaline and circulating sympathin, liberated from stimulated structures, cooperate in augmenting or lengthening the duration of such changes. A brief period of excitement will discharge adrenaline from sympathetic nerve endings, sympathin will come away from the affected organs and also adrenaline from the adrenal medulla. These circulating sympathico-mimetic substances may have effects which outlast for minutes the exciting incident—effects which possibly explain the agitation which is experienced after the object or condition, which produced the excitement originally, has disappeared.

There was a time, about twenty years ago, when a lively controversy was going on between Stewart and Rogoff, then of Cleveland, and a group in the Harvard Physiological Laboratory as to whether the adrenal medulla responds to changes involving the sympathetic system by an extra discharge of adrenaline (Cannon,<sup>7</sup> 1929). The Cleveland investigators themselves furnished evidence that adrenal secretion is under control of the splanchnic nerves, for when they stimulated these nerves they saw a retraction of the denervated iris—a retraction which did not occur if the blood flow through the adrenal veins was obstructed during the stimulation, and which did occur when the pent blood was released. They denied the claims of the Harvard group, however, that afferent stimulation and asphyxia, which are accompanied by a natural discharge of splanchnic impulses, induce a similar increase of the secretion. In 1922, Carrasco-Formiguera and I,<sup>8</sup> using as an indicator the denervated heart instead of the denervated iris, provoked an acceleration of the heart rate by stimulating afferent nerves or inducing asphyxia. When we obstructed the blood flow through the adrenal veins these reflex and asphyxial effects did not occur, and when the pent blood was released the heart was again accelerated. The logic of the situation thus presented required Stewart and Rogoff to accept our evidence for reflex and asphyxial secretion from the adrenal medulla or to repudiate the evidence on which they based the conclusion that the output of

adrenaline is under splanchnic control. That dilemma has not been met in the past seventeen years.

In reports of the work done by Stewart and himself, Rogoff<sup>9</sup> (1935) has repeatedly and insistently laid stress on the fact that they employed a quantitative method. The method involved collecting blood from the adrenal veins as it gathered during a measured time in a section of the inferior vena cava, the so-called "cava pocket," and then assaying the adrenaline content of this blood by comparing its effect and that of various concentrations of adrenaline on a beating intestinal strip. By use of this method the Cleveland investigators obtained results which led them to infer that adrenal secretion is constant and unvarying, indeed, Rogoff has declared that the conclusion that asphyxia and central stimulation induce an extra output of adrenaline "has never been supported by satisfactory measurements of the rate of secretion." That statement indicates disregard for the results obtained by Rapport and myself<sup>10</sup> (1921), and by Sataké and his colleagues<sup>11</sup> (1927) with use of the very method which Stewart and Rogoff devised. For more than a dozen years the Japanese investigators labored in this field. They published a large volume of experimental studies which definitely and quantitatively confirmed the results obtained by the Harvard group and which also clearly explained Stewart-and-Rogoff's failure as being due to too deep anesthesia. Rogoff has not only not attended to this evidence contradictory to his views, he has not attended to the studies of various observers—in Europe, Africa, South America—who with different methods have supported consistently our conclusions. Indeed, in the past twenty years there has been no support whatever, from any quarter, for the claims of the Cleveland pair. I offer no apology for recalling this old controversy, because there still appear in text books and even in a fairly recent publication of the American Medical Association (Rogoff,<sup>9</sup> 1935) statements which lead readers to conclude that the issue is not fully settled and that there is still some question about extra adrenal secretion when the sympathetic system is active.

As I have intimated, in the course of this controversy the denervated heart was used as an indicator of increased adrenaline in the circulation. It is extremely sensitive, responding by a faster beat when the adrenaline concentration is increased by only 1 part in 1,400,000,000 parts of blood. When, with aseptic precautions, the heart has been isolated from the nervous system the animal may live indefinitely, with the heart con-

tinuing to perform its proper functions as a pump (Cannon, Lewis and Britton,<sup>12</sup> 1926) Hence, while the animal is in excellent physical condition, records can be made of the heart rate under various experimental conditions and thereafter the adrenal glands can be excluded from action—by removing one of them and denervating the other—and records of the heart rate then made again under the same conditions Thus, by finding that an acceleration occurred during the tests, and that acceleration failed to occur after adrenal inactivation, we were able to show that muscular work, emotional excitement, asphyxia, low blood pressure, external cold, infection, and hypoglycemia were accompanied by an extra secretion from the adrenal medulla, and extra activity of the sympathico-adrenal system<sup>9 10 11 12</sup> Each one of these situations makes a special demand on the organism or is likely to make that demand In each one of them the operation of the system is such as to favor the welfare of the organism The blood flow is shifted in such manner as to promote effectiveness in muscular effort, the metabolic rate is speeded up when the temperature tends to fall, glucose is liberated from hepatic stores when the amount in the blood is dropping to a low level, the capacity of the blood vessels is adapted to a reduced blood volume In short, as these illustrations indicate, the system promptly and automatically makes adjustments which are required to prepare the organism for temporary exigencies or to preserve its normal internal condition when that is likely to be disturbed Such services performed by the sympathico-adrenal system at times of unusual or critical need I have called its “emergency” functions (Cannon,<sup>7</sup> 1929)

Much of the evidence that the sympathico-adrenal system performs its special services in times of stress was gained by study of animals—dogs, cats, monkeys—from which that system had been wholly removed The possibility of continued existence without any sympathetic nerves may seem surprising, for they belong to what have been called “Lebensnerven” Yet we have been able, quite easily, to keep sympathectomized animals under the quiet and uniform conditions of the laboratory many months—in one instance more than three years—in good health and nutritional status Cats were most thoroughly investigated So long as they were not subjected to stress they appeared quite normal But when they were exposed to heat or cold they were revealed as defective in their ability to maintain body temperature, when they lost blood they were defective in restoring compensatory blood pressure, when they

ran or struggled the blood pressure fell and they fainted, when placed in an atmosphere of low oxygen concentration they collapsed much sooner than animals with the sympathico-adrenal system intact, and when given insulin in amounts readily endured by normal cats they suffered a sharp drop in blood-sugar percentage which would have been disastrous if they had not been rescued (Cannon,<sup>13</sup> 1939) It was interesting to learn that although sympathectomized dogs showed in emergencies effects similar to those shown by sympathectomized cats the effects were not so extreme The difference can reasonably be ascribed to the remarkable physiological developments which the dog possesses as a running animal a much larger lung surface, cardiac capacity and blood volume for his weight than the more indolent cat possesses, in addition to having a higher hemoglobin percentage, a readier resort to shivering when cold and resort to panting when warm Note that in all these respects removal of the sympathico-adrenal system produces no adverse alteration There is one condition in which these advantages of the dog cannot be effective—i.e., in the mobilization of sugar from the liver when an excess of insulin is given In those circumstances the sympathectomized dog is as vulnerable as the sympathectomized cat (Cannon,<sup>14</sup> 1939) It appears, therefore, that the sympathico-adrenal system is called into action in emergencies and has a fundamentally important function in maintaining a fairly uniform condition in the fluid matrix of the organism, the blood and lymph (Cannon,<sup>13</sup> 1939)

The foregoing discussion has been concerned chiefly with the combined functions of the sympathetic division of the autonomic system and the secretion of the adrenal medulla—i.e., with the functions of the sympathico-adrenal system The question arises as to whether secreted adrenaline, itself, has a distinctive use Rogoff<sup>9</sup> (1935) has declared that it does not play an important role in the body and that "no specific function for epinephrine (adrenaline) has been proved" The main argument against the utility of secreted adrenaline is based on the fact that one adrenal may be removed and the other may be demedullated without endangering the life of the animal Obviously the adrenal medulla is not essential to existence There is a difference, however, between being useful and being essential As we have many times demonstrated, the cardiac nerves may all be severed in animals which survive the operation for many months, the nerves are clearly not essential, but is there anyone who would suppose, therefore, that they are not useful? Simi-

larly the survival of animals without the sympathetic system proves that it is not essential, but again are we to conclude, therefore, that it is not useful? In order to know the utility of adrenaline we must consider what changes are wrought by exclusion of the adrenal medulla, quite apart from continued existence.

First, there is the cooperation between secreted adrenaline, neuronal adrenaline and circulating sympathin, already referred to. Actual records show, as previously noted, that a momentary excitement may have bodily effects lasting 15 to 20 minutes if the adrenals are present and only brief effects if the glands are excluded from action. These records prove that adrenaline intensifies and prolongs the influence of sympathetic impulses.

Again, adrenaline has an accelerating action on metabolism. One milligram of adrenaline will cause an increased output of heat amounting to 50 calories. I have already mentioned the evidence, derived from experiments on animals with the heart denervated, that when the body temperature tends to drop, because of exposure to external cold, there is an increased secretion from the adrenal medulla. If the adrenal influence is suppressed and the animals, thus rendered defective, are subjected to the same conditions as before, shivering occurs to a greater degree than when the adrenals were present and able to augment metabolism, i.e., the animals fall back on muscular contraction as a means of producing extra heat.

Another effect of adrenaline which has been reported by a number of investigators—among them Mendenhall and myself<sup>15</sup> (1914)—is that of hastening the coagulation of the blood. When adrenaline is injected this phenomenon occurs, and when adrenaline is secreted, either as a consequence of splanchnic stimulation or as a consequence of excitement, the time of coagulation is likewise greatly shortened. If the adrenal medulla is excluded and the conditions which normally evoke secretion are repeated, the faster clotting does not occur.

Finally, there is the special effect of adrenaline on the liver. In 1928 Riegele<sup>16</sup> described a network of extremely delicate nerve filaments between the liver cells, with offshoots reaching into the cellular cytoplasm. This observation, if correct, would establish a basis for immediate nervous government of liver function. The observation, however, has been questioned. Two years ago Nonidez<sup>17</sup> (1937) reported that the silver method used by Riegele not only may stain nerve fibers but

also may impregnate fine connective tissue strands and thus confuse the picture "Up to the present," Nonidez wrote, "no nervous structure resembling a network has been described in the liver"

The testimony that nerve filaments are not distributed to liver cells is in accord with the evidence that a relatively small dose of insulin induces a swift and unchecked and quite abnormal fall of blood sugar in animals from which the adrenals have been removed, although hepatic nerves are still intact (Cannon, McIver and Bliss,<sup>18</sup> 1924) It is also in accord with observations that emotional excitement does not cause the usual hyperglycemia in animals without adrenals, but again with hepatic nerves intact (Britton,<sup>19</sup> 1928) Supporting evidence was furnished by the experiments which Lissák and I<sup>2</sup> (1939) performed this year It will be recalled that we found an adrenaline-like substance in the ultimate sympathetic neurones, whether these neurones, or parts of them, were isolated or were imbedded in organs, e g , the heart The significant fact appeared, that whereas extracts of liver *blood vessels* raised blood pressure, dilated the pupil and speeded up the heart rate—thereby revealing the presence of sympathetic fibers on them—extracts of liver *pulp* had little or no adrenaline-like action The occasional slight action can be explained as due to the difficulty of removing the pulp from the vessels without pulling away some of the vascular twigs All these observations, taken together, indicate clearly that the liver cells are not subject to direct nervous control

It appears that the liver can play a role in carbohydrate metabolism quite independently, both by taking in and giving forth glucose By a simultaneous determination of the rate of blood flow through the liver and the glucose content of the inflowing and the outflowing blood it has been shown that during control periods the liver secretes glucose, and that when glucose is abundantly supplied secretion ceases and sugar is retained (Soskin, Essex, Herrick and Mann,<sup>20</sup> 1938) In an emergency, however, as, for example, in great excitement or when insulin is abundant, this intrinsic mechanism is not adequate Faster glycogenolysis is required in order to mobilize blood sugar In these circumstances, adrenaline discharged from the adrenal medulla is the effective agent for releasing glucose from the hepatic stores

Because an injection of adrenaline raises blood pressure, by accelerating the heart and constricting arterioles, an idea has prevailed that persistent hypertension may result from overactivity of the adrenal

medulla In a temporary test, as Freeman and Jeffers<sup>21</sup> (1939) have shown, secreted adrenaline may play a significant role in producing a brief experimental hypertension, but that occurred when the heart was denervated and when its acceleration depended on medullomedullary secretion If the heart was normally innervated, the effect was produced quite as well without any participation of the adrenal glands Again we note a cooperation of adrenaline and sympathetic impulses in the sympathico-adrenal system—a cooperation which permits either of the partners to compensate, in this condition, for absence of the other But neither of these partners is necessary for the maintenance of normal blood pressure The entire sympathetic system may be progressively removed and yet vascular tone is well preserved and the pressure is held within the normal range (B Cannon,<sup>22</sup> 1931) This is not a consequence of compensatory secretion of adrenaline, for there is experimental proof that the adrenal medulla does not secrete unless it is stimulated by nervous impulses, except in the rare state of extreme asphyxia (Zwerner and Newton,<sup>23</sup> 1928) The sustained contraction of the arterioles after sympathectomy appears to be due to intrinsic properties of the smooth muscle in the vessel walls

Two types of prolonged hypertension can be produced experimentally one the result of removal of the restraining nerves (i.e., those from the carotid sinus and the aortic arch), as demonstrated by Heymans and his collaborators, the other the result of lessening the blood flow through the kidneys, as demonstrated by Goldblatt and his collaborators (Cannon,<sup>24</sup> 1937) The former type, Heymans and Bouckaert<sup>25</sup> (1936) report, disappears when the sympathico-adrenal system is entirely excluded from action Whether this type ever occurs clinically is as yet unknown The second type—that produced by Goldblatt clips on the renal arteries—is not affected by sympathectomy Freeman and Page<sup>26</sup> (1937) have found that application of the clips induced hypertension in completely sympathectomized animals and that if hypertension had been produced by partial renal ischemia, later removal of the sympathetic did not improve the condition I have felt justified in emphasizing the absence of evidence that excessive adrenal secretion explains high blood pressure because, unfortunately, the idea that the adrenals are the cause of it has prevailed and has led to severe operations directed towards denervating them in order to abolish their supposedly pernicious discharge There is no doubt that if adrenal secre-

tion should be discharged in sufficient amount to produce a high blood pressure it would have other wide-spread and highly disturbing effects on the organism such as are, in fact, not seen in cases of hypertension

In summarizing the part played by the adrenal medulla in the functioning of the organism we may recognize that it cooperates with sympathetic impulses in producing adrenaline, that this sympathico-adrenal system is brought prominently and usefully into action in emotional excitement, in vigorous muscular work, in asphyxia, low blood pressure, chilling surroundings and hypoglycemia—in brief, that it serves effectively in emergencies, furthermore, that this service can be given a general expression in stating that the system guards the constancy of the internal environment of the organism, and finally that secreted adrenaline itself acts to prolong the effects of nerve impulses, to accelerate metabolism, to shorten coagulation time and to release glucose from the liver. There is no evidence that secreted adrenaline is an important agent in maintaining a high blood pressure

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## HYPOTHYROIDISM DIAGNOSIS AND TREATMENT\*

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**T**HE term hypothyroidism obviously signifies a state in which the individual receives less of the hormone characteristic of the thyroid than is required by his body economy for the preservation of health. We are all quite familiar with such clinical varieties of hypothyroidism as cretinism, endemic or sporadic, and the myxedema of children and of adults. We also recognize hypothyroidism following extensive surgical removal of thyroid tissue, or destruction of thyroid tissue by certain types of chronic inflammation.

I have been asked to discuss with you the diagnosis and treatment of these conditions and that I will do but I must say something also of etiology and morbid physiology because it is upon these that sound clinical practice must rest.

Adult myxedema was first described by Gull in 1874 and its cure by the administration of thyroid was contributed by Murray in 1891. It is of interest to note that Murray died September 23, last—the father of endocrine-substitution therapy. It is also worth noting that probably the first patient to receive his treatment in the United States is still alive at the age of eighty-seven. Mrs. B. is now the patient of Alexander Burgess, of Providence, who kindly gives me frequent bulletins of her progress. Her symptoms were first noted in 1888 and her doctor diagnosed Bright's disease and said she could not live six months. In 1892 another doctor, keener in diagnosis and up to date on his literature, diagnosed myxedema and started her on thyroid. She has taken it ever since.

The case of Mrs. B. teaches us the calamity of missing the diagnosis of myxedema. Had it not been made she would have died in 1903 or earlier, because fifteen years seems to be as long as one can live after the onset of myxedema without thyroid therapy. The symptoms and signs of myxedema are so striking, so characteristic, that there would seldom seem

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to be any excuse for missing the diagnosis. The classic picture should be familiar to every doctor, and if when present there can likewise be demonstrated low basal metabolic rate—minus thirty-five or lower—and elevated blood cholesterol, the diagnosis is practically certain. Nevertheless, in our clinic we get patients each year in whose cases the diagnosis has been missed. Often the error is in supposing that the patient has Bright's disease. Doctors thus give us the opportunity to make cures which they could easily have made themselves, and for which they could have got the credit.

A few years ago I would have told you that spontaneous, acquired myxedema of adults is due to primary atrophy of the thyroid, that the effect of this atrophy is to produce a simple athyreosis, the effects of which can be completely corrected by the administration of sufficient quantities of dried thyroid gland. The only reservation I would have made would have been that in patients with arteriosclerosis you must beware of producing angina pectoris by too rapid elevation of the rate of metabolism, with a resulting inadequacy of coronary blood flow.

Today these statements will still hold in most instances, but recent experience has indicated that there are a few cases of what clinically is myxedema in which the etiology is different and the indications for treatment different. These are cases in which the primary fault lies in the pituitary instead of in the thyroid. The myxedema is the result of a hypothyroidism due to lack of stimulation of the thyroid by the pituitary, rather than to primary failure of the thyroid itself. Actually these patients have a form of pituitary cachexia, or Simmonds' disease, but for reasons unknown, the emphasis in their symptomatology is so strikingly on their hypothyroid manifestations that other hypopituitary symptoms or signs escape attention in the clinical evaluation.

Our attention was drawn to this special type of myxedema by the following experience. A woman of forty-eight entered December 1, 1936, with what appeared to be fairly classic myxedema of about ten years' duration. On treatment with thyroid these manifestations disappeared. However, she soon developed new symptoms—nausea, vomiting, fever, psychosis and convulsions, and died on the thirtieth day of treatment. At autopsy there was found fibrosis of the anterior lobe of the pituitary and atrophy of the thyroid, parathyroids, adrenals, ovaries and uterus. These pathologic changes are characteristic of Simmonds' disease and the terminal symptoms are like those sometimes seen in the crises of

Addison's disease<sup>1</sup>

More recently, my colleague, J. Lerman, referred to the hospital a woman of thirty years (U177833), whom he thought had ordinary myxedema. On thyroid therapy she also improved as to her myxedema manifestations, but presently went into an undoubted state of adrenal insufficiency, from which, however, she was rescued by vigorous treatment with sodium chloride.

Although rare, cases of this type are important, because of the hazards of treatment with thyroid. Their detection will depend upon the discovery of evidence of coexisting underfunction of other endocrine glands than the thyroid. In women developing myxedema prior to the menopause the occurrence of amenorrhea, in place of the usual menorrhagia of myxedema, would be very suggestive of the pituitary type. However, there may be no absolute method of recognition except by very careful control of thyroid therapy in all cases of myxedema, and to the well known danger of inducing angina pectoris, we may add the occasional one of producing Addisonian crisis.

The treatment of the usual type of myxedema is so simple that we need not devote much time to it. The objective should be to rid the patient of his symptoms and clinical signs with the smallest daily ration of thyroid by mouth that will accomplish this purpose. Usually this will be found to be in the neighborhood of one to one and a half grains of thyroid U. S. P., once daily. If such dosage produces any sort of untoward symptoms, angina or other, thyroid should be stopped for a few days and then resumed in smaller dosage. We have some patients who cannot tolerate rations of over one-half to three-quarters of a grain a day. During the inauguration of thyroid therapy the doctor, for the reasons given above, should have the patient under close surveillance, and only after the size of the permanent ration has been well established, is it wise to lengthen the time between check-ups.

The treatment of the pituitary type is far from simple. Persons so afflicted are in need of all the functions of the anterior lobe of the pituitary. This might be provided either by administering the anterior lobe hormones themselves, thyrotropic, adrenotropic, gonadotropic, or the hormones which the other endocrines make under anterior lobe stimulation, namely, thyroid, cortin, estrin.

As a matter of fact, in practice good results may probably be obtained in such cases by a combination of small doses of thyroid when the

patient is protected against adrenocortical insufficiency by a high salt intake, and some preparation containing the gonadotropic principles of the anterior lobe.

The effects of hypothyroidism are more serious when the state supervenes before growth has been attained than after. The adult who acquires myxedema, if normal before the disease began, can be made normal again by adequate treatment with thyroid. On the other hand, hypothyroidism during infancy or childhood, if long untreated, will result in physical and mental stunting which no amount of substitution therapy later can altogether alleviate. Indeed, cretinous children, who have reached ten years without treatment, derive little if any benefit from thyroid. About all the effect it has upon them is to make them irritable and less manageable than when in their athyreotic vegetable-like state. The earlier in life hypothyroidism occurs, and the longer the interval before adequate treatment is established, the more grave will be the consequence.

Thus the prognosis in cretinism, that is to say, congenital hypothyroidism, whether of the endemic or sporadic variety, is problematical. Certainly the outlook is brightest when the correct diagnosis is made very early in life and treatment started and maintained throughout the growth period and thereafter. Even so, on the question, whether an absolutely normal mental development can occur, authorities differ.

The early diagnosis of cretinism depends upon recognition of the significance of characteristic facies, habitus and behavior. It can be made in the early months of infancy. Among the earliest signs, as pointed out by Talbot,<sup>2</sup> are a heavy expression, and pig-like appearance of the eyes. A curious yellow tint appears early on the mesial aspect of the cheeks, disappearing when the infant cries. Changes in the tone of the voice in the direction of hoarseness are always important. Later the appearance of the cretin becomes thoroughly characteristic—a round stupid face, wide flat thick nose, open drooling mouth from which protrudes an over large tongue. The neck is short and thick, the trunk short, the belly prominent, always with umbilical hernia, the skin is dry and harsh, fat pads appear about the shoulders, and dentition is delayed.

Laboratory confirmation can be had by demonstration of low basal metabolic rate, elevated blood cholesterol, or by x-ray showing delayed bone age.

As soon as the diagnosis of cretinism is made substitution therapy with thyroid should be started and should be continued in adequate

dosage without interruption throughout life

The criteria of adequate dosage are several. Not only have we basal metabolic rate and blood cholesterol as measuring sticks, but also bone age, height age, and mental age. I agree heartily with Wilkins,<sup>3</sup> who claims that it is not sufficient to maintain basal metabolic rate and cholesterol at normal levels, but that every effort to secure the right growth rates is also essential. To make up for lost time in regard to these, Wilkins points out that it may be necessary to keep the cretin for a time mildly hyperthyroid. In my clinic the experience has been the same.

The magnitude of dosage that may achieve the desired ends is somewhat as follows:

Age	Dosage
2- 4 months	1/10 grain per day
4- 8 "	1/5 grain per day
8-12 "	3/10 grain per day
12-24 "	2/5 to 3/4 grain per day
2- 4 years	1/2 to 1 1/2 grains per day
4-12 "	1 to 3 grains per day

The reports of success with treatment vary. Certainly no amount of treatment will make the cretin more intelligent than he would have been had he not been a cretin, and in the experience of several competent observers, even with seemingly good treatment, a distressing number ofcretins end up with mental ages of not over ten or eleven years, although in other respects they become quite normal adults. None the less a few do better than this, and a mental age of ten or eleven with a normal body is vastly to be preferred to the state of imbecilic dwarfism that would persist if no treatment, or inadequate or unsustained treatment, were given.

When myxedema is acquired in childhood, the child having made a normal growth in all respects up to the time hypothyroidism supervened, the results of treatment are nearly as perfect as in adult myxedema. In order to make accurate predictions of what may be expected of treatment, therefore, it is necessary to distinguish sharply in diagnosis between cretinism and juvenile myxedema. This should not be difficult because the child who has acquired myxedema does not possess the dwarfism and gross habitus of the cretin, but merely the dry skin, puffy-

ness and retardation displayed by the adult with myxedema

In conclusion I urge you to be on the look-out for all types of hypothyroidism, for it is most unfortunate to miss the diagnosis of a curable disease. In treating adults with myxedema, be watchful for untoward effects during the inauguration of therapy, and reduce the dose of thyroid if they occur. With regard to cretins, the important points are very early diagnosis, and sustained and sufficiently large dosage of thyroid throughout life.

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# THE MODERN TREATMENT OF PYOGENIC OSTEOMYELITIS\*

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**W**HEN a new treatment of pyogenic infection such as sulfanilamide is introduced, it is always appropriate to consider it in relation to osteomyelitis because of the high mortality, prolonged morbidity, resistance to treatment, and marked tendency to recurrence, characteristic of this disease. I have not had a great experience with sulfanilamide but I shall take advantage of the occasion to review the general field of osteomyelitis therapy which is the subject of much controversy.

The reason for the difficulties encountered in the treatment of osteomyelitis is to be found mainly in the nature of bone itself. The infection begins within a rigid tube which offers resistance to external drainage and invites spread along the medullary canal with death of bone. The presence of lime salts in the dead bone causes it to be broken down much more slowly than soft tissue and only by the direct cellular action sequestered parts are either extruded or have to be surgically removed. The persistence of cavities, large and small, which remain the seat of infection, leads to a state of chronic osteomyelitis and is responsible for recurrences. The infected bone cannot be completely excised, as in the case of an infected viscus, such as the appendix, because of danger of creating a defect. Another difficulty is that osteomyelitis is due to the staphylococcus in about 90 per cent of the cases and the body is particularly slow to develop an immunity against infection by that organism.

If we review the pathogenesis, the portal of entry of the organism cannot be detected in about 75 per cent of the cases, but in the other 25 per cent it is known to be a local infection usually of the skin, less often in the respiratory tract. In the other 75 per cent it is presumably a small hidden point of infection. Micro-organisms are fed into the blood stream from here, lodging in the sinusoids, or possibly in clumps as small emboli, and setting up infection in the bone. Large septic emboli rarely

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lodge in bone creating massive infarction and osteomyelitis. In some cases bacteria lodge in other structures as well and simultaneously give rise to sepsis. In the great majority of cases this is not so. They set up only osteomyelitis.

The evolution of the osteomyelitic focus is then an extremely variable one. In severe cases it spreads rapidly, destroys the bone extensively, and in turn may give rise to sepsis. From this group of severe cases the grade of inflammation may range all the way down to a localized osteomyelitis with slight local and general symptoms. Because of this marked variation in extent and severity, it is difficult to discuss the treatment in brief general terms and each case calls for more or less individual consideration.

**Septic cases.** Osteomyelitis as a part of a widespread sepsis does not call for operative treatment. It should be treated by fluid administration, by blood transfusions and, in the present opinion of the profession, by sulfanilamide or derivatives. How successful the drug will be is still uncertain but it is doubtful if cures will be effected. Long states that in *staphylococcus* sepsis little is to be expected from its use. If abscesses point they should be drained.

Severe cases that are primarily osteomyelitis fall into two age groups—infants and children, adults.

Osteomyelitis in infants and very young children differs considerably in etiology, pathology and clinical course from that in older individuals and its treatment is somewhat different. It is due to hemolytic streptococci in about 50 per cent of the cases. The lesion is more often localized to the end of the shaft, although multiple involvement is common. A reason for this is that the cortex is thin and permeable and the pus quickly breaks through, forming a peripheral abscess. The children are usually very sick at the onset.

Treatment should consist of fluid administration, blood transfusions, sulfanilamide and immobilization of the affected part. Operation is badly tolerated and should be postponed until abscesses form which should be opened through small incisions. There is rarely necessity for early opening of the bone for drainage of abscess even in mild cases. Dead bone is absorbed rapidly, cavities fill out and in three or four months the bone is restored to normal as shown by roentgenograms.

Severe osteomyelitis in older children and adults should be treated expectantly in its early stages by parenteral fluids, blood transfusions,

sulfanilamide and immobilization In eighteen cases of staphylococcus osteomyelitis treated by sulfanilamide the results were doubtful Very early operation for opening the bone before extension of the infection to the outside has occurred is usually more dangerous than helpful Practically most cases do not offer the surgeon the opportunity of early operation because they are sent to the hospital later after abscesses have formed

Usually pus will localize and appear external to the bone in from three to seven days Aspiration is a helpful adjunct in detecting it When the abscess can be located, it should be opened and drained with small single or multiple incisions and as little anesthesia and blood loss as possible Local anesthesia may frequently be employed However, if the patient continues very ill and external pus does not appear within a few days, do not hesitate to operate, making an opening through cortex and draining the medulla Failure to do so may mean marked spread of the infection and necrosis of the bone, and in some cases the development of septicemia

Milder forms of acute osteomyelitis and especially the localized abscesses in which the general symptoms are not marked call for less urgent treatment, and are usually seen by the surgeon at an even later date than the severe cases As soon as the lesion can be definitely localized with roentgenograms or otherwise, it should be drained and the cavity effaced, as the earlier this is done, the less the likelihood of establishment of a chronic osteomyelitis

Secondary foci of osteomyelitis are common, beginning days to years after the onset of the primary focus

The great majority of them are localized lesions and they often develop with mild local symptoms or even silently I have seen many instances where weeks or months elapsed before they caused local symptoms or a local swelling and where they were discovered incidentally in roentgenograms They should be treated by the same operative procedure as is used for the primary cases

The treatment of the subacute and chronic stages of osteomyelitis is the subject of much less dispute than is that of the acute stage Sulfanilamide usually has no influence on the condition, although I have seen a few cases where rapid healing followed its use By far the most important point is the performance at the earliest possible time of a thorough operation, for the removal of dead bone and the effacement of cavities,

pockets and bone sinuses As much chronically infected bone should be removed as is compatible with preservation of continuity of the shaft Subperiosteal resection results in interruption of continuity so often that it is rarely indicated except in the ribs, upper portion of ilium and fibula where it should be used routinely since the creation of a defect in those regions makes no difference

The type of dressing employed afterward is of minor importance The wound may be packed open for three to six days and afterwards dressed with surface dressings Cast immobilization is indicated in case of large wounds The wound may be dressed with an Orr vaseline pack and a cast applied with changes of the pack every four to six weeks This latter method is often a very annoying and unpleasant form of treatment I can see no fundamental virtue in it and do not use it Cases thus treated heal as well but no better than those treated by the first method

I have said nothing of vaccines, serums, maggots, and bacteriophage in the treatment of either acute, or chronic osteomyelitis None of them seems to have proven sufficiently practical or to have given sufficiently satisfactory results to have won a general and lasting place in osteomyelitis therapy Personally, I do not try to use any of them

In closing, I realize that this discussion of the treatment of osteomyelitis has been very incomplete and I have mentioned few of the technical aspects of the problem but I have tried to select only those features which I considered most appropriate for this program

## OTITIS MEDIA AND ITS EXTENSIONS\*

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**T**HE title of this paper may seem strange to some. It is based on the consideration that mastoiditis, petrositis, labyrinthitis, Bezold's abscess, sinus thrombosis, and brain abscess, as well as meningitis of otic origin, are simply "extensions" of otitis media. The middle ear is the primary focus and also the most important drainage point, hence the emphasis will be on it rather than on other parts.

To understand the chemotherapy of otitis media and its extensions it is necessary to know something of the average course of the disease and something of the development and detailed anatomy of the temporal bone. As every physician knows, the latter consists of relatively flat outer parts called the squamous and mastoid portions from which projects inward a roughly three-sided structure called the petrous pyramid. This pyramid is the most important part of the temporal bone because it forms the keystone of the base of the skull and contains the middle ear and labyrinth. The labyrinth will not concern us in this paper because it is only secondarily involved in infections of the temporal bone. We are here only interested in the primary infections. As mentioned above, these spring almost invariably from the middle ear, although blood stream infections from distant foci have been described.

Simply stated, the external auditory meatus develops from the first branchial cleft, while the middle ear and Eustachian tube develop from the first branchial pouch. The lining of the middle ear cavity, therefore, is made up of mesoderm and entoderm which is continuous with mesoderm and entoderm of the nasopharynx. The ear drum is the partition between the outside and inside invagination and consists therefore, not only of the lining of the middle ear but also of the stratified squamous epithelium which develops from the ectoderm of the embryo. Now at birth, the middle-ear cavity is almost entirely filled with mesoderm, but

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as the individual grows this becomes thinner and thinner, so that in adults the submucosal tissues are so thin that they lie directly on the underlying bone. This single, rather flat-celled layer of epithelium and its underlying connective tissue is therefore often called "mucoperiosteum".

At birth the petrous pyramid, exclusive of the middle ear cavity, consists of bone, labyrinth, fibroblastic marrow and spaces for blood vessels. As the temporal bone grows, the fibroblastic marrow begins to be replaced by air-filled mucous membrane which pushes out in all directions, but most extensively through the antrum, into the mastoid and thence into the squamous portions of the bone.

Just how far this process will go in a given, growing child we have no means of prediction. In the opinion of the author, normal pneumatization of the temporal bone is largely a matter of the hereditary formation of the skull. Perhaps the size of the brain has something to do with it (cf. the studies of Dyke and Davidorf in cases of hemiatrophy of the brain). The generally accepted theory is that of Wittmaack who believes that reduced pneumatization is due to early infection of the mucous membrane which prevents normal invagination of the air-filled middle-ear sac. Others present different theories. Actually, we do not know any more about why some mastoids are large and highly pneumatized than we do about why some feet are big and flat while others are small and arched. There are undoubtedly many factors, some normal, some pathologic, which contribute to the final result. However, it makes a great difference whether the temporal bone is highly pneumatized or not. The great surface presented by many air cells lined with mucous membrane can excrete entirely too much fluid, if inflamed, to evacuate through the Eustachian tube or through a perforation in the drum membrane. Extension of the inflammation and pain due to the pressure are the result. Furthermore, if the temporal bone is extensively pneumatized, there is more chance for infection to become shut off at a distant point where drainage through the middle ear is impossible. It is these cases which often come to mastoid surgery or to surgery deeper in the temporal bone.

It must be remembered, to understand the foregoing discussion, that the middle ear is actually not a small cavity with specific dimensions as is intimated in most text books. Actually, it is almost impossible to measure the capacity of the middle ear because air cells in and around it



Fig 1—Vertical section through four temporal bones at the depth of the round and oval windows showing the variation in the size of the middle ear cavity and the communication of the middle ear cavity with surrounding air cells

vary so tremendously from case to case (Fig 1) When the middle ear becomes infected, these air cells also become infected so that it is impossible to have otitis media without some mastoiditis, and if the petrosa is pneumatized, impossible to have otitis media without some petrositis The air cells allow the infectious processes to involve at once a large part of the temporal bone Their partitions are thin and are normally poorly vascularized, and worse than this, their connections are usually relatively small It is really a wonder that infections of the mastoid so often get well without surgery Furthermore, the air cells, especially in children, abut directly on bone marrow, and in certain types of infection, this becomes involved in the disease It has not yet been ascertained



Fig 2—Photomicrograph showing mild, low-grade inflammation in the niche of the oval window

whether it is the increased vascularization and local leukocytosis of inflammation which permits the body to take care of such poorly drained areas, or whether it is a stifling of the growth of the invading organism by the production of anaerobic conditions. Conceivably all of these factors and perhaps more are responsible.

#### MODE OF INFECTION IN OTITIS MEDIA

The complicated series of cavities in the temporal bone can become infected in a number of ways. In infants, the most usual way is for the nasal secretions to run into the Eustachian tubes as the child lies on his back during an upper respiratory infection. Very small children cannot blow their noses or hawk mucus from their nasopharynxes, and since their Eustachian tubes are relatively short and straight, infection easily



Fig 3—More advanced stage of inflammation in the niche of the oval window. Note increased vascularization and thickness of the mucous membrane about the interior crus of the stapes

enters their middle ears. If they are turned on their bellies, however, it may easily drain out again. There is much less suppurative otitis media in the infant wards where babies are turned over regularly. With older children and with adults, the commonest method of infecting the middle ear seems to be from blowing the nose too violently. Marked sudden changes in pressure, such as those produced by deep diving may also suck infected material from the nasopharynx into the middle ear. Occasionally an ear drum becomes perforated or ruptured, permitting infection from the external canal to enter the middle ear, but even in these cases the usual cause of the infection is the nasopharynx. The perforation in the drum makes it very much easier to blow infected material

into the ear because there is no longer a closed cavity. How much infection of the middle ear takes place through the submucosa of the Eustachian tube due to its contiguity with the nasopharyngeal lining is still a matter of conjecture.

### PATHOLOGY OF OTITIS MEDIA

Regardless of how an infection enters the middle ear, the pathology is at first the same. There is edema of the mucous membrane, which swells five to ten times the normal thickness, then a serous effusion into the cavity. Following this there is a leukocytic infiltration of the submucosa beginning perivascularly and then extending to involve the entire mucoperiosteum. As time goes on, the effusion into the cavity tends to become purulent. At first, polymorphonuclears are quite prominent, but soon very few can be found among the monocytes. As fluid and sometimes gas collects in the cavity, the drum bulges outward and more and more of the surrounding cells become involved. The more virulent the infection in the submucosa, the more quickly the effusions become purulent, and the more reaction produced not only in the middle ear but also in the surrounding air spaces. If the infection is fulminating, the drum either ruptures spontaneously or has to be opened by a surgeon. Drainage is effected, and as a rule there is subsidence of the process in four to thirty days. Very mild processes, however, have been known to subside in twenty-four hours, but occasionally there is a smoldering infection which does not subside for several months. If the infection in the main cavity persists more than a few days, it almost invariably becomes more purulent, spreads and pockets in several places producing a thrombophlebitis of small veins in the mastoid and petrosa and thereby brings about necrosis of the air cell system. Excessive fluids secreted by the mucous membrane may also produce destruction of the bone by direct pressure. Microscopic sections show the mucoperiosteum of both middle ear and mastoid cells to be densely packed with leukocytes and fibroblasts. There is also destruction of the epithelium at various points and consequent invasion of the cavities with granulation tissue. With the breaking down of bone there is always some regrowth of osteoid, but in progressing empyema the regrowth of bone lags behind the breaking down. The cortex of the temporal bone may erode at any point, producing an abscess behind the auricle, over the lateral

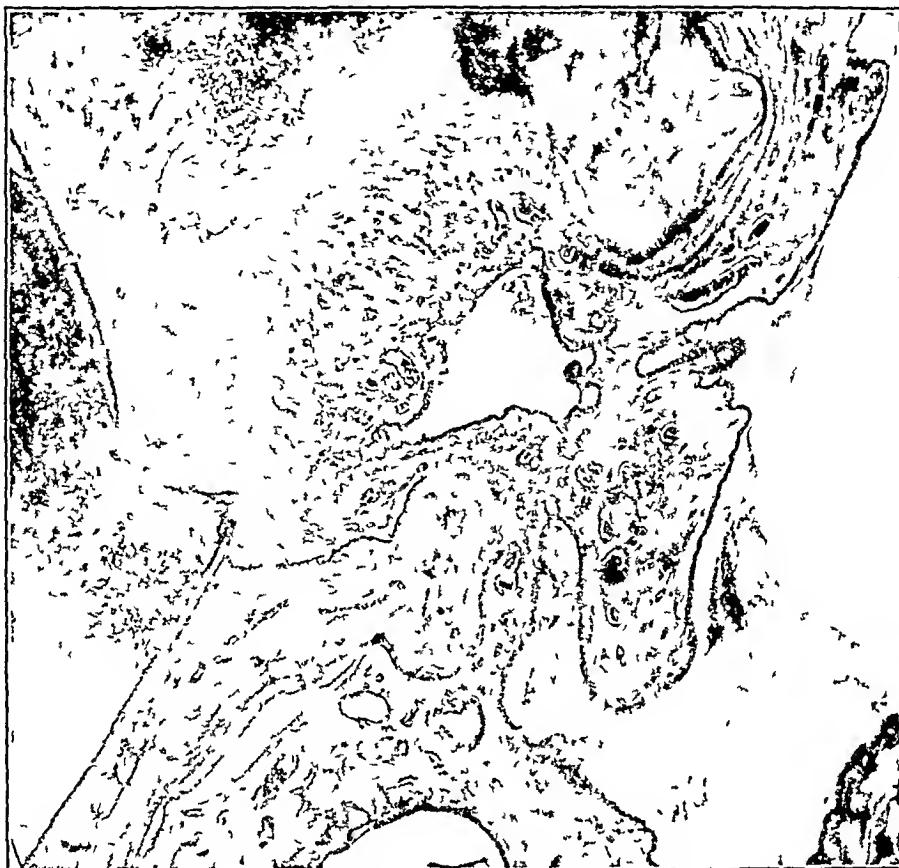


Fig 4—Still more advanced inflammation in the region of the round window and beginning polypoid degeneration

sinus, in one of the cranial fossae, or even in the neck, cheek, or nasopharynx. The more extensive the air spaces, the more chance of infected material becoming caught in some out of the way pocket and so producing a focus which will seek drainage by breaking through the cortex in this way. No matter how extensive the pneumatization, however, there is always some marrow in the temporal bone which is contiguous with the most peripheral air spaces. With infection of the air spaces there is always some reaction in this marrow, and occasionally, especially in young bones, the infection actually invades the marrow spaces, producing an osteomyelitis.

For purposes of simplification, then, the pathology of otitis media and its extensions can be divided into four distinct steps: first, edema of the mucoperiosteum and serous exudation; second, increased vascu-

larization of the submucosa, infiltration with leukocytes, proliferation of fibroblasts and increased purulence in the exudation, third, after two or three weeks, necrosis of the soft tissues as well as the bony walls of the cavity (this can now be seen in roentgenograms), fourth, especially if the process is less fulminating, there may develop polypoid degeneration of the mucoperiosteum and a prolonged, low-grade osteitis and osteomyelitis

Any one of these four processes may stop, regress, and heal, leaving a more fibrotic mucous membrane and organized bands of scar tissue attached to the ossicles. Usually there is some reduction in size of the air cavities which already exist, and in young children infections may inhibit further pneumatization of the mastoid.

With repeated infections the processes are very similar in each instance except that inflammation in previously formed scar tissue produces much less vascularization than in normal tissue. The scar tissue may toughen the drum so that it does not break. Pressure then builds up in the middle ear and spreads the infection more deeply. Furthermore, with the regrowth of bone in the previous infections the connection between the mastoid cells as well as the antrum is likely to be narrowed. This increases the possibility of infection becoming trapped deep within the bone, and explains why complications most often occur in cases with a history of previous otitis media.

#### THERAPY OF OTITIS MEDIA

The treatment of otitis media for the last several decades has been directed towards the provision of adequate drainage for the middle ear and its surrounding air cells. If the infection was mild (so-called "acute-catarrhal" otitis media) drainage was usually obtained by reduction of infected material in the nose and by shrinkage of the Eustachian tube orifice. If the infection was more acute or more purulent, incision of the drum was resorted to. After myringotomy or spontaneous puncture the canal was simply kept clean to promote drainage either with dry wipes or irrigations of various kinds. If these did not suffice and the mastoid was seen to be breaking down in the roentgenogram, a mastoidectomy was performed, usually in the third or the fourth week of the infection.

Since 1936 the use of sulfanilamide and related drugs has been added to our resources. A great many cases show subsidence of symp-

TABLE I  
FACTORS IN OTITIS MEDIA

1 Age	Infants and old people apparently more susceptible
2 Sex	No essential difference
3 Place	Flora and fauna vary in different vicinities
4 Environment	
5 Station in Life	Clinic patients seem to have more trouble than private patients
6 Habits	Blowing of nose, swimming, etc
7 Diet	Vitamins, etc
8 Previous Infection and Immunity to Infection	
9 Mode of Infection	
10 Time	Yearly cycles of incidence, March and April peak, etc
11 General Physical Condition	Debilitating disease Allergy
12 Heredity	Race Susceptibility to infection Anatomy Pneumatization of the temporal bone Type of Eustachian tube Lymphoid diathesis
13 Skill of Physician and of Nursing	
14 Reaction to Surgery	
15 Reaction to Medication	Sensitivity Tolerance Vomiting Excretion, etc Individual Response
16 Type of Infection	
17 Chance	

toms after chemotherapy so that many physicians have come to believe that it is the only treatment for otitis media, and are beginning to use it in every case. Even the lay public often asks that it be prescribed.

The bad results from improperly conducted chemotherapy often reach the hands of the otologist, so that he tends towards the opinion that drugs are of questionable value. Certainly the present ones mask symptomatology, sometimes cause unpleasant reactions, and make the problems of management harder for him. We have, then, on one side the general doctor and the pediatrician who tend to treat all types of otitis media (often even the non-suppurative types) with chemotherapy, and on the other the otologist who uses it only in desperate cases such as meningitis. Which is correct? Is there a middle ground? Is there some

rule which has scientific rationale, and which will work in the majority of cases<sup>3</sup> I believe that the rule can be built out of a study of the normal course of the disease, the pathology outlined above, and the results obtained in various types of cases by various methods of administration

As already intimated, there are a great many factors which may influence the course of otitis media These are summarized in Table I Many have never been thoroughly studied, but a little thought about each one will tend to give it proper significance

A word is perhaps necessary for certain items under Heredity we have listed Anatomy, which is divided into pneumatization (already discussed) and Eustachian tubes, diameter, and curvature Very little is known on this last subject except that certain people seem to have much more trouble with their tubes than others It is also known that excessive lymphoid tissue about the tube seems to be an hereditary trait, and that this tissue tends to stop up the tubes and predispose to otitis media unless proper measures such as adenoidectomy or radiotherapy are used to combat it Certainly the use of chemotherapy has not yet precluded the necessity for adenoidectomy in cases of recurrent otitis media

It may surprise some to see a heading *Susceptibility to Infection* under Heredity The work of Webster at the Rockefeller Institute, however, has definitely established this for mouse typhoid and mouse encephalitis, and the author has found hereditary susceptibility for otitis media in rats which could be bred out of a colony There is no doubt that otitis media seems to run through certain human families

#### TYPES OF INFECTION

Table II shows that we have a specific chemotherapy for less than half of the total number of cases of otitis media For over 35 per cent of the cases are due to the staphylococcus and more than 15 per cent are due to other organisms for which no specific chemotherapy has as yet been developed However, about 30 per cent are due to the hemolytic streptococcus for which we have sulfanilamide, and 12 to 16 per cent are due to pneumococci for which we now have sulfapyridine Study of Table III will show that three-quarters of the pneumococcus and streptococcus cases get well within three weeks without chemotherapy These two tables indicate clearly that the group that needs to be treated with chemotherapy is definitely a small one

TABLE II

 PERCENTAGE OF VARIOUS ORGANISMS FOUND IN PURE CULTURE AT  
 THE COLUMBIA PRESBYTERIAN MEDICAL CENTER  
 IN THE YEARS 1933 TO 1939

Year	Strep Hemo	Strep Other	Pneumo I	Pneumo III	Pneumo Other	Staph All Types	Others
1933 273 cases	31.13	4.39	2.56	6.22	4.02	41.75	9.89
1934 334 cases	35.2	3.3	3.0	5.7	3.6	41.8	7.8
1935 333 cases	31.6	1.8	4.2	8.1	9.0	32.7	9.6
1936 336 cases	33.1	2.6	8.0	11.9	10.4	27.4	6.6
1937 517 cases	38.7	2.5	3.7	5.0	9.3	33.5	7.3
1938 524 cases	26.44	3.66	5.2	4.63	5.5	41.50	11.9
1939 438 cases	36.78	9.1	4.1	5.51	6.4	36.78	10.11
Total 2,755 cases	33.6	2.7	4.45	6.4	7.04	36.7	9.5

TABLE III

 DURATION OF DISCHARGE AND NUMBER OF PATIENTS THAT CAME  
 TO MASTOIDECTOMY OUT OF 455 CASES DIAGNOSED AS OTITIS MEDIA,  
 ACUTE SUPPURATIVE, IN THE COLUMBIA PRESBYTERIAN MEDICAL  
 CENTER FROM MAY 1936 TO MAY 1937

	1-6 days	7-14 days	15-21 days	3-4 weeks	More than 4 weeks	Mastoid- ectomy
Staph 173 cases	26	62	18	27	33	7
Hemo Strep 163 cases	22	42	21	22	26	30
Pneumo 101 cases	16	28	20	12	12	13
Other Organisms 20 cases	4	9	1	4	0	2

In all fairness it must be pointed out, however, that there is a flaw in the above argument. It assumes that the culture reports are accurate. As a matter of fact, the figures are undoubtedly not exact, for unfortunately many of the cultures were taken using a swab without sterilization of the external auditory meatus. (Incidentally it has been shown by Page that throat cultures are often apt to pick up the offending

pathogen more accurately than a careless swabbing in the external canal) However, the cultures described above were all made in suppurative cases, and if one adds to these the non-cultured cases, especially the non-suppurative cases, it is still fair to say that in the present state of our knowledge chemotherapy is indicated for only a small percentage of all the cases of otitis media.

How shall the surgeon discover this small percentage? Can it be determined with our present meager knowledge of the action of the drug and our knowledge of the pathology of otitis media? Lockwood and others have definitely shown that sulfanilamide is less efficient in necrotic lesions, and that the more the necrosis, the less the likelihood that the drug will be sufficiently bacteriostatic to permit the body to annihilate it. As has been pointed out above, very little necrosis—as a rule—occurs in otitis media and mastoiditis, until the second week of the disease. It would seem, therefore, that in simple otitis media one can wait a week or ten days after the onset using the old, simple, mechanical methods of treatment. Then if there is no improvement and the case looks as if it might go on to surgical mastoiditis or a long siege of drainage, the administration of drugs may be begun with every expectation that they will stop the process if given in sufficient dosage. At the end of a week adequate bacteriological and blood studies should be available so that the correct drug can be selected. Analysis of cases treated with sulfanilamide (Table IV) shows that a large percentage of cases treated with adequate dosage, especially those in hospital, get well while those treated with small or short dosage in the clinic show no more tendency

TABLE IV  
APPARENT EFFECT OF SULFANILAMIDE IN OTITIS MEDIA  
IN 100 UNSELECTED CASES

100 CASES		
Postoperative, questionable effect	Inadequate dosage	Adequate dosage
Reaction	31	11
Recurrent	18	3
	18	25

All but four of the cases on adequate dosage were in the hospital.  
"Questionable effect" represents cessation in less than two weeks.  
"Good effect" represents cessation of discharge in less than a week.

to recover than an untreated series (cf Tables III and IV) The cases in which the drug has no effect are usually cases of inadequate dosage Often there is recurrence if adequate dosage is not prolonged well after temperature is normal and drainage has stopped If the drug is started late in the disease it may have no appreciable effect Apparently the drug has less effect in cases where there has been a previous infection

We have much divergence of opinion as to the dangers of chemotherapy Many say that there is virtually no danger, especially in children, and that all drug-sensitive individuals show up on small dosage so that they can be spotted before any serious harm has been done Others emphasize the danger of damage to the kidneys and liver, cite the patients who have died with anemia and leukocytopenia, or speculate on the effect of the drug on the reticulo-endothelial system in the years to come

The physician must decide at the end of a week or ten days whether his case is going on to a surgical mastoiditis or is going to prolong itself enough so that the patient is in danger of acquiring a residual deafness If he is fairly certain of one of these things, the dangers outlined above need hardly be considered Chemotherapy should be instituted as a major procedure, comparable in every way to surgical interference If possible, the patient should be hospitalized, and if not, careful blood and urine studies should be done every two days at home The dosage should be fairly large (Long and Bliss suggest at least 2 mg per kilo of body weight) and kept up for several days after the temperature has come to normal and the discharge behind the drum has ceased If this is not done there will be almost certainly a recurrence of the disease, especially when the original organism is a virulent one

Analysis of successful sulfanilamide-treated cases shows a dramatic subsidence of symptoms within three or four days Most of them have no pain or fever after two days This suggests that if there is no effect within three or four days the drug is not the answer, and that drainage will have to be instituted by one of the well-known surgical methods In advanced or neglected cases surgery is usually essential, but of course may be supplemented by chemotherapy After all, it is impossible to drain every nook and cranny in the temporal bone, and the chemotherapy will produce bacteriostasis in these unreachable regions The combined use of surgery and chemotherapy is especially important in the complications of otitis media such as meningitis, brain abscess, and

inflammation of the walls of the venous channels draining the temporal bone

To recapitulate, given a case of otitis media, chemotherapy should be instigated a week or ten days after the onset of the disease, if the patient does not seem to be getting well without it and a specific drug is available to combat the bacteria of the infection. The chemotherapy must be given in adequate dosage for a considerable period after symptoms begin to disappear and under careful surveillance of reactions and with surgical adjuncts to the therapy in mind. In no case should it be given casually, without cultures and without a knowledge that most otitis media is self-limiting. It must be remembered that the use of bacteriostatic drugs makes the management of the cases harder because the symptomatology of the disease processes is masked.

Some day it is hoped that we will have new drugs for all types of infection, and drugs which can be given without untoward outside effects—then of course, the above working rule for our present drugs will have to be modified.

## OBSTETRICS AT THE NEW YORK ALMSHOUSE AND AT BELLEVUE HOSPITAL\*

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**I**N colonial times the care of mother and child was entirely in the hands of midwives. The midwives of New Amsterdam were no better and no worse than their professional sisters in Holland who aroused the ire of Hendrick Van Deventer. The father of modern midwifery wrote "they do not understand their business," and again he lamented "I cannot sufficiently wonder at the gross ignorance of most midwives." He urged that examination of the bodies of women dying in childbirth be made a matter of law, to find out whether the mother and fetus died naturally or "sadly perished by the carelessness and cruel hand of the midwife."

The midwives of New Amsterdam have been classed by some writers among the Zeikenstroosters or comforters of the sick. The Zeikenstroosters, however, were men and their function was purely spiritual although they occasionally looked after the sick in defiance of an ecclesiastical ruling prohibiting them from practicing medicine.

Improvement in American obstetrics did not take place until just prior to the Revolution when young colonial physicians began to go abroad for study. The eighteenth century was a period of remarkable growth in the specialty. Knowledge of the obstetrical forceps enabled physicians to displace the Sairey Gamps who had reigned so long in the lying-in chamber. The most potent factor in the manifold advances of the period was the rise of the new humanitarian spirit. As part of this the infant welfare movement emerged "In the nurture and management of infants as well as in the treatment of lying-in women," wrote Lettsom in his *Medical Memons* in 1774, "the reformation hath equalled that in the smallpox, by these two circumstances alone increditable numbers have been rescued from the grave."

\* Read January 11, 1939 at The New York Academy of Medicine before the Section on Historical and Cultural Medicine

Among those studying abroad were William Shippen, Jr., of Philadelphia, James Lloyd of Boston and Samuel Bard of New York. They returned from Edinburgh and London filled with inspiration by their contact with great clinical obstetricians like William Smellie and William Hunter. Each one became the pioneer teacher of obstetrics in his community. Dr. Samuel Bard emulating Dr. John Morgan of Philadelphia, organized the medical school at Kings College (later Columbia) in 1769. At the first Commencement he urged in a notable discourse the usefulness and necessity of a public hospital. This address led to the founding of the New York Hospital, which was chartered in 1771 but did not open for the reception of patients until January 3rd, 1791. Delay during the reconstruction period in the re-establishment of the Medical School and the opening of the hospital was undoubtedly due to divided loyalties engendered in the medical profession by the struggle for Independence.

In 1736, a new Almshouse was built on the Commons where the City Hall now stands. Here according to Dr. Robert Carlisle was the primitive trace of Bellevue Hospital. Following the war the Almshouse was utilized for the first clinical teaching in New York. Both Valentine Seaman and David Hosack studied at the city Almshouse which according to Dr. J. W. Francis was "at that time the only institution in New York in which medical instruction was imparted." Dr. Nicholas Romayne, Dr. Benjamin Kissam and Dr. William Moore were visiting physicians and Dr. Wright Post, the visiting surgeon.

We read that Dr. William Moore's attention "was always more specially directed to the practice of Midwifery, in which he acquired a very extensive experience and practiced with great success, keeping a record of all cases which he attended for the year 1781 to 1823, which amounted to nearly 3,000 cases."

A new Almshouse was built on Chambers Street in 1796. Here the first lying-in hospital in New York City was established in 1799. The previous year a severe epidemic of yellow fever had swept the city. Many expectant mothers lost their husbands. Their pitiful condition aroused the sympathy of Dr. David Hosack. Through his efforts the New York Lying-In Hospital was incorporated in February, 1799. A place was secured at No. 2 Cedar Street and an appeal for subscriptions was made in the Commercial Advertiser for July 23, 1799. In the Medical Repository for 1800, under "New York Lying-In" is the note

"We are informed that this Hospital will be ready for the reception of patients on the first of August "

Prior to the opening of the institution on Cedar Street a lying-in ward was opened in the Almshouse Hospital on Chambers Street The Medical Repository for May, 1799 states that

"A lying-in ward has been established in the Almshouse of the city of New York The cases which occur there are numerous enough to answer the purpose of public instruction Accordingly, there is delivered a course of lectures on the obstetric art, including the anatomical, physiological, and practical parts, by Valentine Seaman, M D As this establishment is particularly and exclusively devoted to the education of *females*, it will be easy for *women* who practice, or intend to practice midwifery, to avail themselves of the excellent opportunities which are hereby held out to them "

The following year Valentine Seaman published the first book to appear on the subject of midwifery by an American author On the title page he calls himself Physician Extraordinary to the Lying-In Ward in the Almshouse The little volume bears the quaint title, *The Midwives Monitor and Mothers Monitor*, and the contents are based upon the course of instruction given the previous winter in the lying-in wards of the Almshouse Thus to the forerunner of Bellevue Hospital belongs the honor of establishing the first wards in New York for expectant mothers and of giving the first hospital instructions to women in the art of midwifery

The statement has been repeatedly made that Dr Valentine Seaman gave a course for trained nurses at the New York Hospital in 1800 The sole authority for this is a letter beneath his portrait in which a member of the family wrote that he gave a course of lectures to the nurses of the New York Hospital The lectures referred to were obviously those given during the previous winter in the Almshouse as he himself states in his book

The first outdoor obstetrical service in New York was established by the New York County Medical Society in 1823 On June 2 a committee was appointed by the Society, "to inquire into the cause of the great number of stillbirths in this city" The Chairman of the Committee was Dr Charles Drake, one of the visiting physicians to Bellevue Hospital The Committee was of the opinion that among the reasons for the large number of stillbirths was the abuse of ergot and the fact

"that the practice of midwifery was still too much confined to ignorant and inexperienced attendants" The Committee recommended "the institution of a lying-in charity for the exclusive purpose of attending parturient females at their own homes" In the minutes of the New York County Society are the regulations drawn up for the Out-door Lying-In Charity A group of consulting and attending accoucheurs were appointed for the various districts in the city to attend the poor in their own homes

In order that the new project should be "more effectively guarded against producing injury to any part of the profession who now receive a compensation however small from attendance upon the lower classes of the community," it was decided "that it shall be the duty of the attending accoucheurs to lodge with the Commissioners of the Almshouse a notice of their respective residences, to attend during childbirth, free of all charge, such females of their respective districts as shall produce a certificate from a Commissioner of the Almshouse of their being proper objects of charity, and to report at the ensuing anniversary meeting of the Society the number of cases they have attended, the character of each labor, together with such other circumstances as they shall deem worthy of being communicated"

The out-door obstetrical service functioned for only a short time The New York Lying-In Hospital which had closed in 1822 again opened a ward in the New York Hospital sharing its facilities with the New York Asylum for Lying-In Women established in 1822 The latter institution moved to a house on Marion Street in 1830 and in addition to an indoor service established a large outdoor service It was known as the old Marion Street Maternity Hospital and eventually combined in 1899 with the New York Infant Asylum (incorporated in 1865) The New York Infant Asylum combined with the Nursery and Child's Hospital (incorporated in 1854) to form in 1910 the New York Nursery and Child's Hospital

One of the early New York obstetricians whose name is closely associated with Bellevue Hospital was Dr John Wakefield Francis He was born the year of Washington's inauguration and died the year the Civil War started For years he was *the* doctor of New York City and his big bushy head was as familiar as the City Hall While still a student of Dr David Hosack whose partner he later became, Francis helped establish the *American Medical and Philosophical Register* The delight-

ful tone of this early magazine was due in a large measure to the literary ability of Francis. His scientific attainments were perhaps few but he was a popular teacher and to his associates in the profession he was "our beloved Francis," a man who was, according to Jacobi, keen eyed, warm hearted, plain spoken and generous minded.

Dr Francis' house, No 1 Bond Street at the corner of Broadway was the rendezvous for all the leading lights of the city. His book of reminiscences, *Old New York*, is a storehouse of information about the last days of Knickerbocker New York. There are many amusing stories about Dr Francis. He continued to bleed his patients long after most of his confrères had given up the practice. Once during a dinner party at his house he suddenly left the table and called his wife to an adjoining room where he proceeded to bleed her. In answer to her protests he said that he perceived that she was about to suffer a stroke of apoplexy and deemed it best to avert it!

Dr Emmet tells an interesting story about Dr Francis. One of his best patients had been delivered of a baby when he had not even suspected pregnancy. He had been sent for at the time of the event but being away from home, someone in the neighborhood had attended the case. "Damn these hoopskirts," Dr Francis exclaimed, "there was a time when I went to church that I could look around me and form some idea of what my income might be during the year. But now, since the invention of these damn hoopskirts, I can no longer judge of the condition of the women. I am away from home when wanted, and some young whipper-snapper is called in and gets the case."

Dr Jacobi tells how, when he first started practice, Dr Francis stopped him on the street one day. "They speak well of you," he said, "and you will get on, only people want sometimes some outward show. Now I am an old man, and you will not mind it when I say you ought to have another tailor." Jacobi replied, "you see, Dr Francis, you are an old doctor, and famous, and you can afford to wear the old-fashioned clothing of the eighteenth of Brumaire and of the century of William Penn, but I cannot afford yet a better tailor."

Dr Francis was one of the editors of the *New York Medical and Physical Journal* which was established in 1822. In the first number, one finds several contributions on obstetrics by Bellevue doctors. Francis himself contributed an article on *Phlegmasia Dolens*. Dr Jacob Dyckman, one of the visiting surgeons to the Almshouse, wrote on a *A Case*

of Tumour within the Pelvis Preventing Parturition Dr William Moore reported *A case of uterine hydatids* The following year Francis published a letter from John D Hunter who while a captive among the Indians west of the Mississippi made some interesting observations on female diseases occurring among the squaws There is also an interesting report by Drs Francis and Beck of the first cesarean performed in the state of New York, the patient operating upon herself and recovering

In 1825, Dr Charles Drake, physician to the Bellevue Establishment reported *A Case of Erostosis of the Os Ischium Impeding Delivery* The patient died of ruptured uterus

An interesting article appeared in 1840 entitled, *A Report of Cases of Puerperal Fever Occurring at the New York Almshouse*, by Alexander F Vache, M D , the resident physician The disease appeared on January 12 Of eighteen women confined in the Almshouse nine had fever and seven died The next six women were placed in the Nursery Of these five had fever and five died Patients were then confined in the building devoted to negroes, out of twelve deliveries, four had fever and four died The obstetrical service was now moved to apartments in the "middle house" of the "lunatic asylum" on Blackwell's Island Here there were twenty-three deliveries with six cases of fever and three deaths The total death rate during this epidemic was 31 per cent The treatment was cupping and leeches Among the assistants at Bellevue was Dr Thomas F Cock who wrote a little *Manual of Obstetrics* and became the first president of the New York Obstetrical Society

Dr D Meredith Reese made a very full annual report of the Bellevue Hospital for 1848 He states that from 1845 to 1848 inclusive there were 678 births in the hospital with seventy-nine stillbirths, a rate of over 10 per cent During the year 1848 there were 208 births with twenty-four maternal deaths of which nineteen were from puerperal fever There were five forceps cases and six cases of embryotomy Note that there were more destructive operations than forceps cases Obviously a low operative incidence resulted in the loss of many babies Fear of infection apparently deterred the doctors from interference and for the same reason cesarean section was not considered Rupture of the uterus followed by death of the mother occurred not infrequently From the meager records available for the twelve years from 1848 to 1859 inclusive it is apparent that the maternal and fetal death rate was

extremely high. The maternal death rate averaged ten times greater than the present rate for the city of New York and in some years it was actually twenty or thirty times greater. Puerperal infection was the chief cause of death but death from eclampsia was also common. The mortality at Bellevue was not greater than in similar institutions, there was a frightful mortality in home deliveries not only in the city but in the rural districts.

In the second half of the nineteenth century a notable group of obstetricians was associated with Bellevue Hospital. Among these were Fordyce Barker and George Elliot. They introduced the use of the hypodermic syringe in America in 1856 and 1858. They deserve our remembrance also for their defence of the use of anesthesia in obstetrics at a time when it was greatly opposed. Elliot wrote, "I would not practice medicine another day if I did not possess the power of relieving pain."

In 1876, Fordyce Barker became the first president of the American Gynecological Society. His book, *The Puerperal Diseases*, which appeared in 1874 had a deserved popularity. Barker with his immense clinical knowledge held peculiar views on the cause of puerperal infection. At the famous New York Academy of Medicine meeting in 1857 he maintained the view that it was an essential fever. Twenty years later while agreeing that it was contagious and praising the work of Oliver Wendell Holmes, he still held that the symptoms of puerperal infection were essential and not the consequence of any local lesions.

T. Gaillard Thomas was connected with Bellevue Hospital for many years. Next to J. S. Parry he did more than anyone else in this country to clarify the problem of ectopic pregnancy. He was the first in the United States to complete an extraperitoneal cesarean section. Isaac E. Taylor was a great clinical teacher and founded the Bellevue Hospital Medical College. Along with Elliot he was noted for his skill with the forceps.

With the rise of scientific medicine after 1850 the history of Bellevue Hospital becomes a part of the main current of medical history. It is probably fair to state that the influential leaders in the movement spreading from France and Germany to America were Bellevue men. The closing decades of the nineteenth century might indeed be characterized as the golden age of Bellevue for on the staff of the hospital and teaching in the medical college were the open-minded Austin Flint, Theodore

Janeway and Francis Delafield, the fathers of pathological anatomy in America, Stephen Smith and Hermann Biggs, pioneers of public health, and William Welch who was eagerly teaching the new germ theory of disease. On the surgical staff along with Smith were William Stewart Halsted, Frederick S. Dennis and Lewis Atterbury Stimson.

The big problem facing the hospital at this time was the control of infection both in surgery and obstetrics. There now appeared upon the scene a man who perhaps did as much as any other single person to make obstetrics a scientific procedure in America. William Thompson Lusk studied at Heidelberg and Berlin two years previous to 1861. At the beginning of the Civil War he returned to America and entered the Union Army. Out of his Civil War experience came his *War Letters* which were privately printed in 1911. After the war he studied at the Bellevue Medical College and then pursued further work at Edinburgh, Paris, Vienna and Prague. After a period of teaching physiology at Long Island Medical College and at Harvard he was appointed in 1871 professor of obstetrics and diseases of women and children at Bellevue Hospital Medical College, a position he held until his death.

In 1872, puerperal infection destroyed twenty-eight women of 156 who were confined in Bellevue Hospital and in 1874 from January 1 to June 11, out of 166 patients thirty-one died of infection. Lusk at this time published a clinical report on the lying-in service in which he urged the building of a separate hospital for the reception of lying-in patients. His advice was not followed but instead in 1875 the lying-in department was transferred to Blackwell's Island where two wooden pavilions were erected and placed in charge of the Charity Hospital staff. Arrangements were made by the city for several private hospitals to receive patients who came to Bellevue after labor had begun. Soon, however, these institutions refused to admit such patients. Thereupon these unfortunate women were delivered on board the transfer boat while awaiting transportation to the Island. They were attended by one of the house staff and one of the nurses from the new training school but no other provision was made for them.

At the International Medical Congress held in Philadelphia in September, 1876, Lusk read a paper entitled *On the Nature, Origin and Prevention of Puerperal Fever*. He stated, "that the capacity of self-multiplication which septic fluids possess has been found to be coincident with the presence of certain organic bodies termed variously micrococci,

muciospores, or sometimes less specifically bacteria" This statement elicited a great deal of hostility Most teachers still believed in spontaneous generation and gave themselves scant concern about the views on puerperal infection advanced by Holmes and by Semmelweis Lusk a few years before had heard Seyfert speak scoffingly of the misfortunes which had clouded Semmelweis' later years, asserting that his doctrines had long before been proof sufficient of his insanity

Present as a guest at the International Congress was Lister himself who according to Lusk was listened to by a curious but unsympathetic audience Lister visited Bellevue Hospital and complimented young Dr Stephen Smith on his success with the antiseptic method

Lusk himself at this period believed that there was a non-infectious form of puerperal fever due among other things to moral causes His conclusion in regard to the infectious form, however, was that "prevention is best accomplished in hospitals by the adoption of Lister's principles," and that "the question of personal responsibility cannot be too strongly impressed upon the medical profession"

In 1877, the attention of the Grand Jury was called to the lack of facilities for obstetrical cases at Bellevue Hospital As a result the Emergency Hospital was established at 26th Street, between Second and Third Avenues in a building which had been used as an engine house by the Fire Department In this makeshift hospital Dr William T Lusk and Dr William M Polk began the fight to conquer puerperal infection

Credit is due to Dr Henry J Garrigues for demonstrating for the first time in America in the wards of the Charity Hospital on Blackwell's Island what could be accomplished by rigid aseptic and antiseptic technique Immediately after his first publication in 1883 Lusk introduced his methods at the Emergency Hospital and subsequently reported that there had been the greatest possible change in his service From October, 1883 to August, 1884 there were no deaths from puerperal infection in 168 cases Dr W L Richardson at about the same time introduced the new technique at the Boston Lying-In Hospital with startling success

In 1881, Lusk's great book on *The Science and Art of Midwifery* appeared and was translated into the French, Italian, Spanish and Arabic

Lusk did the first successful hospital cesarean section in the United States Harris wrote "looking into the past records of New York City

and of the United States at large, of ten hospital cesareans in our country, Dr Lusk's case is the first to recover up to 1887, he is the first to save both mother and child in all the history of New York, the only one of seven operators to meet with success using the Sanger Method in the United States "

Lusk died in 1897 The Emergency Hospital continued in operation until November, 1908 when Pavilions A and B of the new hospital were opened with provision for two obstetrical wards.

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DEATHS OF FELLOWS

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Lynch, John Burgess 17 West 74 Street, New York City, born in New York City, May 2, 1861, died in New York City, December 2, 1939, graduated in medicine from New York University in 1886, elected a Fellow of the Academy, October 6, 1898

Dr Lynch was consulting surgeon to the St Francis and Nyack Hospitals and surgeon to the Hermann Knapp Memorial Eye Hospital

Rogers, John 177 East 71 Street, New York City, born in New York City, Febru-

ary 19, 1866, died in New York City, November 19, 1939, received the degree of A B in 1887, and Ph B in 1888 from Yale University, graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1891, elected a Fellow of the Academy December 7, 1905 and served as a member of the Committee on Admissions from January 1910 to January 1915

Dr Rogers was emeritus professor of clinical surgery at Cornell University Medical College and consulting surgeon to the Booth Memorial, Bellevue, New York Infirmary for Women and Children, St Francis, Ruptured and Crippled and Memorial Hospitals, and the Stamford Hospital in Connecticut. He was a Fellow of the American College of Surgeons and the American Medical Association, and a member of the New York Surgical Society and the County and State Medical Societies

BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



MARCH 1940

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PRESIDENTIAL ADDRESS\*

MALCOLM GOODRIDGE

JUST one year ago, I reviewed the history of The New York Academy of Medicine, and emphasized the fact that throughout its ninety-two years there had been continued progress. I said at that time that we want to be in a position to do even better work than we have in the past, because, as we grow in years, we take on new responsibilities. We cannot remain static, we go either forward or backward.

In some respects, the Academy has made greater contributions during the past year to public welfare, to the welfare of medical education in general, to the welfare of its Fellowship, than ever before in its history.

In other ways, however, this has been a disappointing year. The finances of the Academy continue to be a matter of great concern, and, because of the necessity for balancing the budget, we have been forced to curtail our activities to such an extent that there is a prospect that we shall not be quite so efficient during the current year as we have been in the recent past. This curtailment of activities in every department has been forced upon us, because the requested budget for 1940 so far exceeds the Academy's income. I regret to say that only a small percentage of the Academy Fellowship has given the Fund-Raising

\* Read January 4, 1940 at the Annual Meeting of The New York Academy of Medicine

Committee its enthusiastic support, either through direct financial contributions or by making individual efforts toward increasing Academy endowment

Your Budget Committee has had a good deal of advice as to how the budget might be balanced. It has even been suggested that one activity might be dropped entirely. I can tell you that, if all three of the Standing Committees of the Academy were abolished, with their paid staffs, the surplus remaining after the budget had been balanced in this manner would be scarcely over five thousand dollars. And then, one day, the question might again be raised, as to whether the Academy was properly an educational institution, or if it was not rather a private institution maintaining a library and section meetings for the benefit principally of its Fellowship. That would render us open to investigation on the part of various government agencies, to show cause why we are not subject to income and social security taxes, state unemployment insurance contributions, and real estate taxes, and, under those circumstances, if such taxes were applied, we would have to close the doors of the Library to all but Fellows, and undertake thorough reorganization of the entire staff of the Academy.

So we find ourselves in a serious position, faced with the necessity to curtail the activities of various Standing Committees of the Academy and the Library, by cutting ruthlessly their requested budgets for 1940, which must entail the loss of competent, well-trained employees of long standing.

I am not in any way exaggerating the dilemma in which we find ourselves. Be assured, we are going to carry on, carry on with all the enthusiasm which the various Standing Committees and their staffs have shown in the past, in spite of these handicaps. We are not planning at the present time to abolish any Standing Committee, and we hope this will never become necessary.

I think I have made it perfectly plain that, if the Academy is to go on with its service to the public, we shall have to have more endowment. During the last two or three years, a very hard-working Fund-Raising Committee has managed to raise funds sufficient to help carry the burden. It has not been possible, however, to add most of the funds thus raised to endowment, they have in large measure been paid out for current expenses. This is a hand-to-mouth existence which cannot be permitted to go on. We shall need additional endowment, if we are to

continue to accept our responsibilities as we have in the past, and if we are to continue to develop our capacity for public service in normal fashion

In the review of the activities for the past year, there is, I am thankful to say, a brighter side

#### COMMITTEE ON LIBRARY

The Library activity has continued at an increased pace during the year. There has been an increase in readers over any other year, there has been such a steady increase in bound and unbound volumes that the stacks are now filled to capacity, and the catalog drawers are almost filled. The need for a new stack-room, costing in the neighborhood of three hundred thousand dollars, grows constantly more acute. Unless such an addition is forthcoming, many valuable reference books must be stored, and hence made unavailable to Fellows and other readers.

Because of the lack of adequate Library staff, some details of cataloging have had to be dropped entirely. There are still groups of books which have been in our Library for a number of years and have not been cataloged.

During the year, donations of books were received from many individuals and organizations.

So that you may have a clear idea of what our financial situation is, as it affects the Library, in respect to income, I would say that we have not been able to come within twenty thousand dollars of meeting the requested budget of the Library Committee.

I think most of us have come to realize that the word, *academy*, in its modern sense, and as applied to the Academy of Medicine, connotes an institution of learning, or, if you prefer, an association of individuals for the cultivation and advancement of science and for the elevation of the standard of medical education. The value of such an institution varies in direct ratio with the size, growth, and working efficiency of its library. The Academy Library is being very materially crippled by lack of funds.

#### COMMITTEE ON PUBLIC HEALTH RELATIONS

The Committee on Public Health Relations has rendered its usual public service to the health and welfare problems of the community. Perhaps the outstanding accomplishment of the year of this Committee,

with the financial support of the Josiah Macy, Jr., Foundation, was the two-day round table discussion of convalescent care, from its medical and socio-economic aspects

This Committee has also studied such a variety of questions in the interest of public health as tuberculosis hospitals, one grade of milk, the conference on marriage consultation centers, the control of prostitution, the evaluation of school lunches, open-air classes in schools, health department personnel, physical standards for admission to training courses for police and firemen, the revision of the Physician's Pocket Manual at the request of the Bureau of Census, the health of adolescents

Advice and assistance have been given in various ways to health, hospital, and municipal civil service commissions, and in relation to health standards for the Board of Education. It has also given much consideration to bills introduced into the Legislature, as affecting public health

#### COMMITTEE ON MEDICAL EDUCATION

The Committee on Medical Education sponsored the Twelfth Annual Graduate Fortnight, in October, last year. This Fortnight has become an important feature of medical education in this city. The Graduate Fortnight last year was far and away the most successful of the twelve thus far held under the auspices of this Committee. The attendance was greater, and, in spite of the expense involved in such an important Fortnight, with its accompanying exhibit, the Fortnight finished with an actual positive balance. In other words, for the first time, this Fortnight was not an expense to the Academy, it paid its way, and had something left over.

This Committee was also responsible for the Friday afternoon lectures, lectures on obstetrics, and supervision of Sections, all of which have been maintained at the usual high standard of recent years. The Committee also publishes the Surgical Bulletin, and maintains the Bureau of Clinical Information.

I am happy to report that the subscriptions to the Academy Bulletin received from non-fellows have increased in number, from a little over two hundred to well over three hundred, in the last twelve months.

The very high standard set in recent years by the Subcommittee responsible for the programs of the Stated Meetings has been held

**COMMITTEE ON MEDICAL INFORMATION**

The Committee on Medical Information is just a year old, as a Standing Committee of the Academy. It has rendered many important services as a liaison between the Academy and the public. In this department, some five thousand inquiries were handled during the year, twenty-five per cent of them from physicians, and of this twenty-five per cent, forty-three per cent were from Fellows of the Academy of Medicine. Thus, eighty-nine per cent of the total inquiries came from sources outside the Academy Fellowship.

The Committee has arranged and chosen the speakers for the laity lectures, in which the public has shown sufficient interest to fill Hosack Hall to capacity, and often to overflowing. It has also arranged for the delivery of fifty-two Academy radio periods on a coast-to-coast network through WABC. It instituted a study of the broadcasting of medical education by medical organizations, with the aid of a fellowship grant from Rockefeller Foundation. It has rendered services to an imposing list of organizations too numerous to mention.

It has rendered important service to the public, and has entirely justified its elevation to the rank of Standing Committee of the Academy.

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The report of the Committee on Activities was accepted by the Council, and most of its recommendations have already been acted upon.

An important change in the By-Laws has been suggested, and has already been approved by the Council. It will be submitted, with other amendments to the By-Laws, to the Academy for approval at a later date. This particular proposal eliminates the Membership class in the Academy, and makes all Members, Fellows, and necessitates the abolition of the Committee on Fellowship.

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I have tried to give you a brief outline, so that you may be acquainted with the activities of your Academy. I said a year ago that I hoped we might stir the consciousness of the people as to the significance of the Academy as a public health counselor. I still hold that hope, for the writing on the wall is obvious enough, that if we cannot demonstrate to the satisfaction of people that the Academy is necessary to the public welfare and therefore deserving of financial support, we cannot continue to discharge our full responsibility to the community.

It is my firm conviction that the reason we do not attract more general financial support from outside our walls is that the public remains uninformed as to our objectives and our accomplishments

I am sure much can be done toward keeping the Academy functioning *pro bono publico*, if all those who derive benefit from the Academy's activities, including the Fellows, will make the effort to impress these facts upon the community's consciousness

Before I close this annual statement of the affairs of the Academy, I wish to express a word of appreciation to my immediate predecessor in office, a friend of half a century, James Alexander Miller, for his ever-ready willingness to lend me his ear and to give me wise counsel

It has been for me a very happy year, due in large measure to the enthusiastic cooperation I have received from the entire Academy staff, and to the fine state of morale which exists among them

Working with the new Director of the Academy has been a source of particular joy to me. In less than a year, he has proved himself in every way entirely worthy to fill the office whose standards were set by the immortal Linsly Williams and continued by John Hartwell. I consider this the greatest tribute I could possibly pay your Director, Herbert Wilcox

# PHYSIOLOGY OF THE TESTES AND THERAPEUTIC APPLICATION OF MALE HORMONE<sup>1\*</sup>

CARL R. MOORE

Professor of Zoology, The University of Chicago

Two principal functions characterize the testes and these are recognized to be cooperating agencies in insuring effective male participation for the continuance of the race. The primary function of germ cell production is phylogenetically the older and the hormone secreting capacity a gradually developed, or intensified adjunct, that is responsible for promoting the functional cooperation of accessory reproductive organs that have become increasingly complex as evolution has occurred. Of perhaps equal importance for racial existence are the psychobiological phenomena that constitute the sexual drive, or mating instinct. Granted all other phases normal, the absence of a mating tendency in males would preclude racial existence. Aside from some of the primates, especially man, the lack of testis hormone largely eliminates sexual behavior and even in man the hormone plays a decided role, but to what extent is difficult to define.

## SPERMATOGENETIC ACTIVITY

Avoiding for the moment considerations of embryonic development, the testicle passes through a period of slow progressive maturing which is usually accelerated just prior to spermatozoan formation. The age of this attainment is variable in different species, in the rat spermatozoa appear about the 40th day after birth whereas in man the comparable period is close to the 15th year. In the vast majority of vertebrates, spermatozoan production is strictly a seasonal event, this periodic phenomenon largely characterizes the lower vertebrates but it holds likewise for the greater number of mammals. In the ground squirrel of the mid-west (*Citellus tridecemlineatus*) emergence from hibernation in April reveals the testicle in high spermatogenetic activity and quantities

<sup>1</sup> Several of the investigations referred to here have been aided by a grant from the Rockefeller Foundation to The University of Chicago.

\* Presented November 2, 1939 at The New York Academy of Medicine in the Twelfth Graduate Fortnight.

of spermatozoa are present. By June or July sperm are few or absent and by September the aspermatic testicle is approximately 1/20th the weight of the breeding testis. During December and January, in hibernation or in the laboratory, testicular activity is renewed. Thus for more than half the entire year the testicle is essentially an inactive organ.

Intermediate types bridge the gap between this very short seasonal type and the continuously active type of testis possessed by the rat, rabbit, guinea pig and man. In this group gametogenetic activity is continuous from its beginning to decline or extinction—a period which is probably no more strictly dated than the occurrence of a subnormal function on the part of a heart, kidney or stomach. The testicles of one man may cease to manufacture spermatozoa at 40 years, in others not until the 50th or 60th year, whereas some men of 80 years or above may continue to produce spermatozoa in large quantities.

The classical investigations of Smith<sup>1,2</sup> and of Smith and Engle<sup>3</sup> approximately a dozen years ago revealed to us clearly, for the first time, the specific dependence of gonadal activity upon the pituitary gland and strikingly demonstrated that the sex glands were not autonomous organs, capable of regulating their own activity, but were really organs whose structural and functional welfare was at the mercy of their humoral environment, this may include such elements as specific nutrients (vitamins, etc.) as well as activating substances or hormones.

Numerous investigations involving all the vertebrate classes have now clearly emphasized the testicular dependence upon pituitary secretions. If the pituitary body is removed through operation, germ cells are not thereafter produced but the introduction of fresh gland tissue or proper extracts into the pituitary-less animal restores the capacity to form germ cells. Administration of pituitary substance, or extracts, as well as activating substances from other sources, to prepuberal animals has in many cases revealed the capacity of the gonad to assume maturity functions long before it normally does.<sup>3</sup> In mammals, in particular, this has exhibited itself as a stimulation of hormone secretion more than of spermogenetic activity but in lower vertebrates spermatogenesis has been precociously stimulated by treatments with pituitary substance or extracts in amphibia, birds and to some extent in seasonal mammals. Careful studies on the rat<sup>4</sup> and on monkeys<sup>5</sup> have revealed no evidence of hastening the onset of spermatozoan formation by any treatment. The clinical literature has thus far failed to mention precocious spermato-

genetic responses in man

The demonstration of the prime role of the pituitary in controlling spermatogenetic activity has in a sense shifted the enquiry into basic regulating forces in control of spermatogenesis from the testicle to the pituitary body. In the seasonally active mammal Wells<sup>6</sup> has demonstrated that reproductive inactivity lies not in lack of capacity of the reproductive system to function but is caused by pituitary failure to produce the necessary stimulating force. During the inactive season reproductive stimulants applied artificially for periods of a few weeks will return the testicle and all parts of the system to a breeding state, but the pituitary gland, though a powerful stimulating agent during the sexually active season, reveals only a low stimulating capacity in the sexually inactive period. Contrasting the continuous, and the seasonally active, rodent types it becomes apparent that in the one there is a continuously active pituitary and in the other an intermittent or seasonally active gland.

Enquiry into the factors governing activity of the pituitary, as a solution to seasonal reproduction, provides us with but scanty information. Some element of the environment, or a group of elements, must represent the ruling forces. Rowan<sup>7</sup> clearly demonstrated, and numerous researches have extended the conception, that relative lengths of the light period to darkness play an important part in reproduction in birds and some mammals. Rowan produced a progressively longer day by means of electric lights after sundown, and as the total daylight period began to approach that of the normal spring breeding period his wild captive bird (Junco) showed increased testicular activity and spermatozoan formation during mid-winter when temperatures of -40 degrees F prevailed, control birds without added light showed inactive testes weighing but a small fraction of the weight of testes from light treated birds. Researches of Bissonnette,<sup>8, 9</sup> Benoit<sup>10</sup> and other investigators have extended the findings to several other birds and some mammals. Benoit not only demonstrated the effectiveness of added light to be through the eye but also that light conducted by a quartz rod passing through the orbit to the pituitary body initiated activity in this gland, which activity in turn was the cause of stimulation of development in the reproductive system. The pituitaries from light stimulated ducks implanted into immature female mammals awakened activity in the reproductive system in contrast to ineffectiveness of pituitaries from ani-

mals not exposed to added light. Relative duration of light therefore is one factor in the environment operating to control pituitary activity in some animals but surely other elements are important and some animals may fail to exhibit reproductive responses to added illumination. Wells<sup>11</sup> determined that when ground squirrels were transferred to a constant low temperature in a breeding state, they maintained this active state for periods of a year whereas all field animals had undergone reproductive involution within a period of two months, presumably retention of the breeding state for unusually long periods in the cold was due to retention of activity in the pituitary gland. Other environmental factors such as temperature changes, in contrast to absolute temperature, appear to induce modifications in the reproductive states. On the whole our information with regard to the forces governing pituitary activity is not extensive. The evidence is strong that testicular injuries induced through withholding vitamin-B requirements, or through inanition, represent a fundamental alteration in pituitary activity.<sup>12</sup> Sex gland hormones likewise influence pituitary physiology, and consequent testicular activity, as will be pointed out later.

A recognition of the basic pituitary control over the gonad suggests that diminished or severely curtailed testicular function may be due in large part to defects elsewhere than in the reproductive system.

Spermatogenetic activity of the testis is influenced by other things than pituitary secretion. Radiations of various kinds are known to destroy the germinal elements hence lack of germ cells is to be expected. In mammals possessing a scrotum the failure of testicular descent, or retention of testes in the abdomen, makes it impossible for germ cell formation.<sup>13</sup> The cause of the aspermatic condition has been revealed through many experimental analyses to be the abnormally high temperature of the abdomen. The scrotum is recognized as a local thermo-regulator effectively reducing the temperature of the testicle and this function is essential to the production of germ cells.<sup>14</sup> The closure of the excurrent outlet from the testis, by severing or ligating the vas deferens, has been alleged to result in destruction of the germinal tissues and to prohibit further spermatogenetic activity. This contention deserves passing mention, only because of the continuous resurrection of the idea from the literature of ten to thirty-five years ago. More than a hundred years ago the English physician and surgeon, Sir Astley Cooper,<sup>15</sup> proved conclusively on his own dog that closure of the outlet

passages for periods of three to five years, closure being confirmed at autopsy, left the testicle normal in size and actively producing germ cells. Repeatedly during the past twenty years the vas deferens has been closed without abolishing spermatogenesis in several species of birds and at least eight species of mammals, including rats and man, closure of the passages existed for periods of months, and years in the case of man.<sup>16</sup> Separate pieces of the testicle existing as a transplant from one animal to another, hence without ducts, have continued spermatogenetic activity in amphibia, birds and mammals. The rate of new formation of sperm, after vas closure, may be somewhat reduced, and local areas of destruction and resorption may occur temporarily, probably due to excessive pressure from retention, but when resorption relieves the condition, renewed activity follows.<sup>16</sup> We can agree that vas deferens ligation is an effective sterility measure but only by preventing egress of formed cells and not from lack of capacity to produce them.

### TESTIS HORMONE

Although it has been known since Biblical times that early loss of the testicles occasions marked differences in man and other mammals it is less than 100 years since Berthold<sup>17</sup> demonstrated this to be due to a humoral mechanism.

When we survey the problem of testis hormone in its entirety we are forced to attribute the chief significance of the secretion to its capacity to condition the organism successfully to carry on its part in reproduction. Nature apparently did not have in mind cosmetic phenomena, a specific sleep producing mechanism, a means of prolonging life, sharpening of wits, nor any specific aid to digestion, when testis hormone was provided for. Successful performance in reproduction involves among other things a control of function of the accessory reproductive organs, this function provides a means of transport for spermatozoa, their introduction into the female, as well as stimulating the desire to mate with receptive females. The condition of the various accessory reproductive organs serves as a means of indicating the hormone state of the animal, the condition of the comb in cocks, the microscopic character of seminal vesicles, prostate glands, vas deferens, Cowper's gland, etc have all been employed to denote the presence or absence of testis hormone.

It should be recalled that for the majority of vertebrates the animal

is a going concern throughout the year while the reproductive system may be in a functional condition for periods of but two to three months

In point of contrast we may refer to animals that secrete hormone continuously and to others in which such secretion is limited to a very short period. In the first case the accessory reproductive organs and mating instinct are fully developed throughout the year and the animal functions in reproduction in any month, whereas in the latter type such conditions prevail perhaps for less than two months and the males at other times of the year are in essentially a castrate condition. The various lines of evidence show clearly that the endocrine function, as well as the gametogenetic function, depends upon the pituitary gland.

In constant or seasonal producers of hormone, pituitary removal causes immediate loss of hormone secretion and effectively prevents further secretion as long as there is an absence of a gonadal stimulating substance.

With reference to the period of hormone secretion it has thus far been impossible to set a very definite beginning. The question whether embryonic testes secrete a hormone that is responsible for the development of the Wolffian ducts is a problem receiving much attention at the present time. In my estimation the majority of the evidence inclines to deny it and if this estimate is correct it would place the beginning of testis secretion in postnatal life, the exact time varying with different species. In the rat evidence points to the 35th to 40th day as a period at which hormone secretion is sufficiently under way to attain an effective threshold for seminal vesicles. Similarly, in other mammals various postnatal periods exist subsequent to which definite signs of beginning puberal changes become evident. In man the studies of prostates throughout life by R. A. Moore<sup>18</sup> give indication of definite testis secretion from the 10th to 13th year of life. Androgens have been recovered from the urine of boys at ages from three to five years, with gradually increasing quantities up to fifteen to twenty years<sup>19,20,21</sup> but it is not certainly established that recovery of androgenic substances from the urine of children indicates clearly the effective release in the body of internal secretions from the testis.

Once established, hormone secretion is a continuous process in several species, including man, and intermittent with seasons in the majority of vertebrate species, until the declining period of its production, this latter period is less well circumscribed than its onset. In the rat no one

has yet obtained males so old that age alone has clearly limited this activity. The oldest rats studied by Romeis<sup>22</sup> which were older than three years—a period much beyond the average span of a rat's life—were in possession of accessory organs larger than those from younger vigorous animals. Such conditions of accessory organs are proof of strong testis hormone secretion. Wiesner<sup>23</sup> failed to find any correlation between extreme age and external manifestations of senility and hormone secretion. In man, R. A. Moore<sup>18</sup> found evidence from prostates of the loss of hormone secretion in some cases by the 50th year, but just as good evidence from others of 80 years that testis secretion was in good order. General physiological states throughout life may modify hormone secretion at any period yet to link so-called senility changes with diminution of hormone secretion in any causative manner is to go beyond the known facts.

It is to be emphasized that hormones secreted by the testis are not stored in the body but are rapidly lost through utilization, breakdown or excretion. Mature rats reveal definite cytological changes in the accessory organs within two or three days after testis removal.

Aside from loss of secreting tissue—which can follow diseases, radiations or removals—the greatest known single factor modifying testis hormone secretion is the pituitary gland, and many imposed conditions that result in loss of hormone secretion appear to be indirect effects through pituitary interference. Inanition, or vitamin-B deprivation leads to a loss of testis hormone secretion<sup>12</sup> but they likewise produce relative inactivity in the pituitary.<sup>24,25</sup> In such deficient males hormone secretion is immediately reinitiated, without dietary correction, by such gonadotropic agents as exist in pregnancy urine or the pituitary. In a similar manner seasonally inactive males lose their testis hormone secreting capacity at a time when the pituitary gland shows a diminished capacity to stimulate the reproductive system of immature females. Such males will secrete hormone intensely if only they are treated with a gonadotropic agent.<sup>6</sup> Any condition, therefore, that involves pituitary inactivity will naturally lead to diminution or loss of testis activity.

Hormone secretion can be carried on by testicular tissue located at any point in the body as a viable graft.<sup>17,26</sup> The mere transfer of testis tissue into a new locality, however, does not constitute a viable graft even though firm nodules may be palpable. Unless the tissue remains viable, after such transfer, no physiological effect can be expected ex-

cepting some unknown effect that may possibly come from the autolysis of any tissue, since the amount of hormone carried over by even an entire testicle is too small to be detected by the most sensitive indicators known.<sup>27</sup> Viable grafts cannot be expected unless the transplanted tissue is from the same species<sup>28</sup> and the alleged effectiveness, for long periods, of ape testis implants into man can be discounted.

Cryptorchid or undescended testes do secrete hormone even though gametogenetic activity is entirely absent. Instead of greater hormone secretion by the undescended testicle, as formerly contended, the production is less in testes artificially elevated into the abdomen as well as those occurring normally.<sup>28,29</sup> Whether this is due to an effect of the higher abdominal temperatures, injurious to the gametogenetic function, or to unknown factors, is yet to be determined.

Vasoligation, as a rejuvenation measure, was popular but a short time past, the idea behind it being based upon the supposition that hormone secretion was increased thereby and that secreted hormone served as a rejuvenation instrument. Long preceding the introduction of vasoligation for alleged rejuvenation purposes, subsequent to 1920, it had been shown incontrovertibly that ligation of the excurrent passages from the testes did not cause degeneration of the germinal epithelium or an increase in interstitial tissue. All contentions of an increase in hormone secretion were based upon subjective criteria. The recent investigations of Poynter<sup>30</sup> on the rat have convincingly demonstrated that the operation is without effect on hormone secretion whether the duration of closure has been weeks, or many months, or longer than a year—a period in the rat much beyond one-third of the animal's entire life span.

#### ISOLATION OF THE MALE HORMONE

A brief recall of the spectacular advances in the last fifteen years in the isolation of the male hormone may be of interest. McGee<sup>31</sup> in 1927 succeeded in preparing the first unquestioned potent extract of the testicle. The lipoid fraction of fresh bull testis provided an impure extract which caused growth of the capon's comb<sup>32</sup> and it proved capable also of repairing castration damage to all accessory reproductive organs of the rat, substituted for the spermatozoon life-maintaining property of testis secretion, and prevented loss (or reestablished) the power of guinea pigs to perform ejaculation upon electrical stimulation on the head.<sup>16</sup> Further purification of testis extracts by Gallagher and Koch finally

resulted in a highly concentrated activity In 1929 an androgenic substance was obtained from human urine by Funk and Harrow<sup>33</sup> and by Loewe and Voss<sup>34</sup> which likewise substituted for testis activity Following the concentration of the active principle in human urine the brilliant chemical work by Butenandt and co-workers<sup>35,36</sup> resulted in obtaining a pure chemical substance, androsterone, whose chemical nature was determined from a very small quantity of crystals With the proposed formula assigned by Butenandt in mind Ruzicka and co-workers<sup>37</sup> in Switzerland immediately prepared the substance by synthetic means from cholesterol A second substance having androgenic properties, dehydroandrosterone, was likewise prepared from urine concentrates<sup>38</sup>

The comparative activities of androgenic substances from urine and from testis tissue on experimental test animals was emphasized especially by the Laqueur group in Amsterdam<sup>39</sup> and differences in the resistance of the active substance from the two sources to boiling alkali<sup>40</sup> indicated that different chemical activities were obtained from the two sources Further chemical work in Amsterdam finally led to the preparation of a pure chemical substance from testis tissue, testosterone, by David and others<sup>41</sup> Almost immediately its production by synthetic means was announced by the Butenandt and Ruzicka groups<sup>42,43</sup> Noting that the effectiveness of testosterone was enhanced by the addition of tissue extracts from testis or other organs, themselves inactive (so-called X-substances), a large number of esters and other compounds of the parent hormone were prepared and proved to possess androgenic activity in varying degrees Thus, there is available at present more than a score of pure chemical substances that exert androgenic activity when introduced into the organism<sup>44,45</sup> One of the most active compounds is testosterone propionate, the substance most usually employed for clinical use It is current belief that the internal secretion naturally supplied by the testicle in life is perhaps quite similar to testosterone, perhaps in some peculiarly effective chemical combination It must be admitted, however, that the naturally secreted hormone is not known for certainty and neither is it known whether different species produce different chemical substances as their internal secretion from the testis Physiologically, testosterone, t-propionate, androsterone and other substances maintain the accessory reproductive organs of castrated mammals in a state entirely similar to that in the normal animal though the quantities of the different substances necessary to maintain normality vary to a

great extent, one substance may be more than ten times as effective by weight as another pure substance

Administration of the chemically pure androgens for the most part has utilized the subcutaneous or intramuscular injection of solutions of the chemical substances in a light oil. Oral effectiveness has been of low order but recent advancements give promise of some improvement in effectiveness when taken by mouth. Suspensions of the compounds in a lanolin base with application as cutaneous ointments is an effective procedure, some compounds thus administered are more effective than subcutaneous injections.<sup>46</sup> Ointments of testosterone, methyl testosterone, and t-propionate are all effective as cutaneous ointments and essentially in the order as given.<sup>47</sup> Deanesly and Parkes<sup>48</sup> demonstrated that implantation of pure crystalline substances beneath the skin provides probably the most efficient method of application. The ideal sought is naturally the slow but continuous release of the active principle into the circulation, and the greater effectiveness of such compounds as t-propionate is believed to reside in the retarded absorption from injection sites.

#### NUMBER OF HORMONES

The question of a multiplicity of hormones secreted by the testis has received considerable attention but in my estimation substantial evidence for the production of more than one substance is yet to be presented. In the rat it is fair to state that no known change dependent upon naturally secreted hormone has resisted repair by a pure chemical compound such as t-propionate.

#### EFFECTS OF ADMINISTRATION OF ANDROGENIC SUBSTANCES

The effects of administration of androgenic substances depends to some extent upon the state of the animal receiving treatments. Speaking in general terms for experimental animals (1) these substances in the developing animal lead to modification of sexual differentiation, particularly in developing females, females of developing chickens,<sup>49,50</sup> rats,<sup>51</sup> mice,<sup>52</sup> and opossums<sup>53,54</sup> are modified in many ways. Complete male duct equipment may be produced in females, copious amounts of prostatic tissue may be caused to develop in females that normally never exhibit the prostatic homologue, and the female external genitalia may be caused to develop into typical masculine type (2) Administration of androgenic substances to immature males induces precocity that

involves all duct and glandular structures of the reproductive system, in some species the testis appears to exhibit precocious development whereas in other species definite and pronounced injury follows Precocious puberty, a term applied sometimes unfortunately, will perhaps convey the general effects here indicated Chicks out of the egg only two weeks respond to male hormones by lusty crowing and attempts at treading their immature mates whether the substances are secreted by the testes as a result of gonadotropic treatment<sup>55,56</sup> or injected direct<sup>57</sup> (3) Administration to males below par in their sexual states can result in greatly stimulated responses<sup>58,59,60</sup> Extra-seasonal males can be returned to the breeding state in short order Low copulatory responses can be replaced by decided activity Underdeveloped accessory organs of reproduction—prostates, seminal vesicles, penis, etc.—are increased in size (4) Administration to adult castrated males prevents regression of the accessory organs if it follows castration immediately, or repairs the involuted castrate organs that are dependent upon such secretions These hormones enhance, or maintain, or stimulate, as the case may be, the sexual drive (5) Administration of androgenic substances to females has a variety of effects In the normal female estrus cycles and ovulation are abolished, ovaries are frequently luteinized, menstruation is inhibited Male psychic tendencies are frequently induced and female rats adopt the masculine sexual responses, female canary birds are induced to sing and their social order is materially advanced, courtship is of a masculine type<sup>61</sup> Mammary glands and uterus are often stimulated During pregnancy androgenic treatment may be followed by death, resorption or sexual modification of young, parturition is postponed and lactation is essentially abolished

Various other additional effects could be mentioned but it is sufficient, perhaps, to realize that though these substances play an important role in normal masculine sex life, untoward effects may follow their application as an ordinary drug

Of particular interest here, are the effects of androgenic substances in man Of what use are they clinically, in what type of patient should they be employed, what is proper dosage, how administered, what contra-indications exist? The general statement that the clinical limitations are not yet completely defined can pave the way for certain suggestions arising from hormone applications in man, guided often by our knowledge of effects in experimental animals

It will no doubt suggest itself immediately that individuals devoid of testicular tissue through lack of proper development, atrophy or castration would be proper subjects for therapy. By such means lack of maturity changes associated principally with a high pitched voice may be expected to show modifications. Alleviation of castration or eunuchoidal conditions reported by clinicians, usually after subcutaneous or intramuscular injections, have largely followed a general sequence in which earliest noticeable changes have been the initiation of, or more frequent, erections sometimes characterized by severe priapism, growth of the penis, induction of, or increase in, ejaculations, growth of genital hair, prostate, increased salt, water and nitrogen retention with resulting gain in weight, some change in pitch of voice and less frequently, perhaps, growth of beard. After the principal puberal changes have been developed, retrogressive changes of more evident nature do not appear rapidly with discontinuance of hormones, but involution of accessory reproductive organs does occur. It is to be appreciated, however, that the maintenance of a typical functional state is dependent upon continuous administration. Daily dosages of 25 mgs t-propionate have been found effective, as well as dosages divided to approximate 50 to 60 mgs per week.<sup>62 to 68</sup> Analysis of the urine of eunuchoids or castrates reveals an increase in excreted androgens during administration and the recovery of activity has been reported from 14 per cent to 70 per cent, the variations being due in part to an estimate based upon different urinary compounds.<sup>69,70,71,72</sup>

The question of effects of administered androgens upon the testicle is not settled. Against the supposition that testis hormone would stimulate testicular activity Moore and Price have emphasized the injurious effects upon the normal testicle from administration of these hormones to normal young rats.<sup>73,74,75</sup> Short periods of treatment reduced the weight of testicles by 80 per cent, and caused severe histological damage and an entire cessation of spermatozoon production. It was suggested that androgens stimulated the accessory reproductive organs direct but that inhibitory effects of the hormone upon the pituitary was the pathway of the harmful effects of androgens upon the testicle, hence an indirect one. The report of lack of reparative effects upon testicles degenerate because of hypophysectomy, or other causes of damage, while the accessory organs were stimulated was one line of evidence suggesting that androgens had no direct action upon the testicle. These

observations have been substantiated but the fact that androgen administration immediately following hypophysectomy, before damage appeared in the testicle, prevents testicular involution that would otherwise follow has reintroduced the question of testicular stimulation by androgens<sup>76,77,78</sup> There is the added fact that androgenic substances administered to the quiescent seasonal breeding male cause resumption of testicular activity<sup>79</sup> These phenomena require further analysis The fact that hypophysectomy damage is equally well prevented by yeast extracts<sup>80</sup> and by progesterone,<sup>81</sup> and that the protective action of various androgens does not parallel their androgenic potency<sup>78</sup> raises seriously the question of the validity of the evidence suggesting a stimulating influence arising from the testicle upon its own physiological functions

In addition to the harmful effects upon the testicle of the rat similar injuries have likewise been reported after androgenic treatments in dogs,<sup>82</sup> ducks,<sup>83</sup> cocks<sup>84</sup> and guinea pigs<sup>85</sup> In man the effects of administered androgens upon the testicle are reported as suggestive stimulation, no apparent effect, or injurious effects Heckel<sup>86</sup> has recently pointed out severe reduction in spermatozoa in man during injection of t-propionate, with recovery after lapse of administration, and this receives confirmation in the work of McCullagh,<sup>87</sup> repeated periods of injection are followed by severe reduction in sperm counts

Androgens have been administered to boys in attempting correction of testicular undescendence Whereas some favorable effects are reported the question has other aspects Precocious development of external genitalia and development of other maturity phenomena introduce questions of the advisability of such ministrations<sup>88,89</sup>

The treatment of prostatic hypertrophy through administration of androgens has been recommended but opinions are variable on the advisability of the procedure or benefits derived The treatment has been advocated on the assumption that older men secrete less androgenic materials and that the disturbed normal balance of androgen-estrogen permits estrogenic substances to stimulate prostatic hypertrophy Suggestions for its use arose largely from the work of the Laqueur group<sup>90</sup> and the clinical experiences of van Cappellen<sup>91</sup> Zuckerman<sup>92</sup> has discussed the experimental basis suggesting the treatment and the recent literature review of Vädgoff<sup>93</sup> portrays the experiences of a number of workers Thus far the chief claims for benefit from the treatment rest almost solely upon symptomatology, or clinical improvement,<sup>94</sup> and no

one to my knowledge has claimed reduction in size of the prostate. It is reported that administration of t-propionate for periods up to 95 days fails to alter the histological character of the benign hypertrophied tissues.<sup>95</sup> It would seem fair to suggest that in man prostatic hypertrophy has not been shown to be accompanied by increased urinary estrogens, or the administration of androgens to lower estrogenic output, it has not been shown that estrogens in man are in any way causally related to prostatic hypertrophy, finally, it is scarcely probable, on theoretical grounds, that androgen administration would in any way reduce the size of the prostate. The value of the treatment would appear to be an unsettled question perhaps with the weight of evidence pointing to the negative.

In a discussion of the therapeutic application of male hormone brief mention should probably be made of its use in gynecological practice. Some clinicians have considered it advisable to attempt modifications in pituitary activity by means that would avoid the effects of administrations of estrogens, hence androgens have been tried in various disorders in women. Favorable results have been reported in the inhibition of lactation during the puerperium,<sup>96</sup> amelioration of dysfunctional uterine bleeding,<sup>97,98,99,100</sup> and in menopausal disturbances.<sup>101</sup> Prolonged usage however may be responsible for the induction of undesirable characters such as voice changes, unusual growth of hair or excessive growth of the clitoris.<sup>102</sup>

It is apparent that the general subject of therapeutic administration of the male sex hormone is still in the experimental stage and requires the maturing influence of time and experience before its real value and limitations are established.

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## THE PHYSIOLOGY OF THE OVARIES\*

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IT IS WELL recognized that the ovaries have a double function, the formation and periodic liberation of sex cells and the secretion of the female sex hormones, the estrogens and progesterone, which play an important role in the maintenance and cyclical changes of the accessory reproductive organs. It is also clear that the ovaries are not self-maintaining structures. Certain hormones of the anterior pituitary are essential to their maintenance and in turn the secretions of the ovaries influence the secretion of the gonadotropic hormones and probably other hormones of the hypophysis.

The inter-relations of these various structures have been intensively studied in the clinic and experimental laboratory for more than a decade. Although they appeared to be simple at first and in their basic outlines are simple, yet they have many complex features which even at the present time are but imperfectly known. Evidence for this last statement can be gained by even casual examination of results obtained in any sterility clinic, or of experimental work directed towards the re-institution of fertility when sterility has been induced by the experimental ablation of the hypophysis. We also have, perhaps, been too inclined to believe that the ovarian hormones act solely on the accessory reproductive organs, whereas in fact these secretions are powerful agents which certainly influence many other body mechanisms, perhaps all of them.

The developmental and later cyclical changes of the structural components of the ovary need, as an introduction, to be only hastily reviewed. At birth an immense number of ova are present. Figures differ somewhat but show that there are between 100,000 and 400,000 in the human ovary at birth. Between birth and puberty many of these disappear but there still remains a large number at the onset of sexual maturity (Schroeder<sup>1</sup>). In addition to this initial number, most recent investiga-

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tions indicate that there is a formation of new ova from the germinal epithelium throughout the reproductive period (Allen,<sup>2</sup> Evans and Swezy<sup>3</sup> and others), although this is not universally accepted as being true (Kingsbury<sup>4</sup>) In the human, all ova are destined to mature or to undergo degeneration and destruction by or shortly after the end of the reproductive period, for within a short time after the menopause none can be found nor can follicular development be stimulated by the injection of gonadotropic hormone It is evident that but few of the ova and their enclosing follicles have undergone complete development, the number of eggs that normally mature during the entire reproductive period of a woman not exceeding some 400 Thus most of the original thousands of primordial follicles degenerate at some stage in their life cycle, not infrequently after they have undergone considerable growth or indeed after they have reached nearly mature size In most mammals the theca interna of those follicles which undergo atresia form cords or masses of epithelioid-like cells, the so-called interstitial tissue of the ovary In rabbits in which this type of tissue reaches the greatest development, the ovaries are laden with these cells and they were designated as the puberty gland by Ancel and Bouin That these cells can excrete estrogenic hormone in lower forms is evident from work on hypophysectomized rats In old-world monkeys and humans, however, interstitial tissue is very scanty or absent and it is difficult to attach any secretory role to it The hyalinized bodies which form from atresia of follicles in the human can hardly be suspected of having a secretory function

The changes and differentiation of various parts of those follicles which are destined to undergo maturation and ovulation are well known, and will not be reviewed It will suffice to refer only to the fact that during this growth two structures are differentiated which, in addition to the ovum, could, from their structure, be expected to form secretions These are the epithelial lining of the follicle, the granulosa, and the inner layer of the enveloping connective tissue capsule, the theca interna The cells composing the latter enlarge and assume epithelioid characteristics during the growth of the follicle It has been thought that the follicular fluid which, as first shown by Allen and Doisy et al<sup>5</sup> in 1924, contains estrogenic hormone, was probably formed by the granulosa Corner,<sup>6</sup> however, has recently reviewed the evidence in regard to which cells form estrogen and has come to the conclusion that the connective tissue element, the theca interna, and not the granulosa, is the site of

### ovarian secretion of estrogenic hormone

Following rupture of the follicle and extrusion of the ovum at ovulation profound changes take place in the follicle, resulting in the formation of a new structure, the corpus luteum. This newly formed structure secretes a second sex hormone, progesterone. Although a subject of debate at first, it now seems certain that corpora lutea also secrete estrogen.

In addition to the secretion of estrogen and progesterone, there is secreted by the human female a large amount of androgen, as shown by the urinary assays from the laboratories of Koch,<sup>7</sup> of Laqueur<sup>8</sup> and of Callow.<sup>9</sup> That the ovaries may be the site of secretion of a part of this hormone appears probable. The experimental work of Hill<sup>10</sup> in mice and of Deanesly<sup>11</sup> in rats has shown that ovarian grafts made into the ears of castrated males maintained the male accessory reproductive organs if the animals were placed in a cool environmental temperature. Due to their exposed position, the temperature of the transplanted ovaries was more influenced than they would be in their normal location. When the animals were kept in a warm room the accessory organs atrophied and assumed the condition characteristic of the castrated male, indicating that no androgen was secreted by the ovarian grafts. However, the evidence indicates that in women the most important site of formation of androgen is not the ovaries, but is probably the adrenal cortex. Hamblen et al.,<sup>12</sup> using the colorimetric method of Oestung, found normal androgenic titers in five oophorectomized women and Hirschmann<sup>13</sup> chemically isolated dehydroandrosterone and androsterone from nine ovariectomized women in only slightly lower than the yields reported by Callow and Callow.<sup>14</sup>

Although estrogen is found in the blood and urine in ovariectomized women, as shown by Frank et al.,<sup>15</sup> Fluhmann<sup>16</sup> and others, and estrone and progesterone normally occur in small amounts in the adrenals, it seems safe to assert that the effective estrogen and progesterone in non-pregnant women are formed in the ovaries, as evidenced by the profound involution of the accessory reproductive organs after ovariectomy. Where the estrogen which is found in the blood and urine after ovariectomy comes from is an unsolved problem, but the adrenals are a likely source.

Before taking up the physiological actions of the female sex hormones—the estrogens and progesterone—I will discuss in as simple a way as

possible the number of natural estrogens which occur, their structural formulae and the transformations which they undergo before being excreted in the body, or in other words, their metabolism. It is known that but little of an injected estrogen can be recovered from the urine and feces. Furthermore, much that can be recovered is in an inactive form. It has been conjugated and in order to render it again biologically active it must be hydrolyzed. The site in the body where this inactivation or detoxification takes place will also be discussed. I do not find in the literature a simplified description of the chemistry of the estrogens and it seems that an attempt to give such a description might be of value to those who are interested in the sex hormones but who, like the speaker, are not chemists.\*

A very large number—running into the hundreds—of estrogenic substances are now known. Their structural formulae have been determined and they have been synthesized in the laboratory. They can be separated into those which occur in nature, or the natural estrogens, and those which do not occur naturally, but which are produced only in the chemical laboratory. Most of the latter are of low potency, although some give a reaction with small amounts of material, as, for example, stilboestrol. Only seven estrogens are known to occur in the tissues and fluids of animals. Of these seven, five are not found in the urine of women but occur in the urine of pregnant mares. Three only (estrone, estriol and estradiol) are found in the urine of women. The third one named—estradiol—has only recently been isolated from the urine of women and occurs in very small amounts. It has also been isolated from the urine of pregnant mares and, more important from the point of view of the metabolism of the estrogens, from the liquor folliculi of sow ovaries. Doisy and his group<sup>17</sup> in 1935 having isolated 11 mg using more than four tons of sow ovaries to secure this small amount of chemically pure hormone. Since this substance is the one chiefly found in the ovaries, it is thought to be the parent hormone of estrone and estriol, the two other hormones isolated in humans. The naturally occurring estrogens all have the same carbon skeleton, the cyclopentenophenanthrene nucleus (Figure 1). This same skeleton is found in other biologically active substances, bile acids, toad-poisons, androgens, adrenal cortex hormone, progesterone, and the sterols. The differences between these substances

\* Invaluable assistance was received from Dr. Louis Levin in the preparation of the discussion on the chemistry of the estrogens and progesterone.

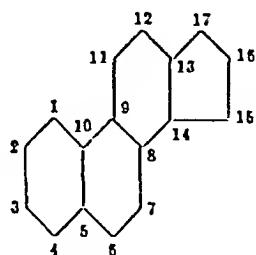


Fig. 1—The carbon skeleton (cyclohexenophrenanthrene nucleus) of the naturally occurring estrogens and other steroid hormones, showing the numbering of the carbon atoms

are due to different side chains and groupings attached to a common skeleton, and to certain space relationships. However, the difficulty of synthesizing the estrogens is much greater than it is with the androgens, progesterone and desovycorticosterone. The latter are prepared commercially from the natural sterols such as cholesterol. The so-called pseudosynthesis of estrone from ergosterol has been reported but because of the cost of ergosterol and the small yield, it is not a practical method of obtaining estrone. The total synthesis of equilenine, an estrogen found in the urine of pregnant mares, has recently been reported by Bachmann, Cole and Wilds,<sup>16</sup> and since equilenine can be reduced to estradiol the commercial synthesis of this substance appears to be a possibility. All the natural estrogens now in use come from urine, largely from the urine of pregnant mares. This urine yields largely estrone and this by reduction is changed to the more potent compound, estradiol.\* Other substances may be substituted in one of the side chains, to give a more prolonged action, as for instance, estradiol benzoate (the commercial product called Progynon B), or estradiol dipropionate (Figure 2).

Chemically the three estrogens differ from each other only in the groupings on carbon 16 and 17 (Figure 2). Estradiol, the most active and probably the true follicular hormone, has an alcohol group on carbon 17. In estrone this alcohol group is replaced by a carbonyl (ketone) group. If the elements of water are added to estrone at the carbonyl group, estriol results. It is evident, then, that these three compounds are very closely related. In fact, some of the interconversions

\* Estradiol occurs in two forms,  $\alpha$ -estradiol and  $\beta$ -estradiol, the differences being due to the space relationships of the OH group on carbon 17. The  $\alpha$  form predominates in the isomers obtained from the reduction of estrone to estradiol. This is fortunate for those who desire to make potent commercial preparations because the  $\alpha$  form is much more potent (some 30 times) than the  $\beta$  form. Most commercial products of estradiol contain only the  $\alpha$  form, the  $\beta$  form having been eliminated.

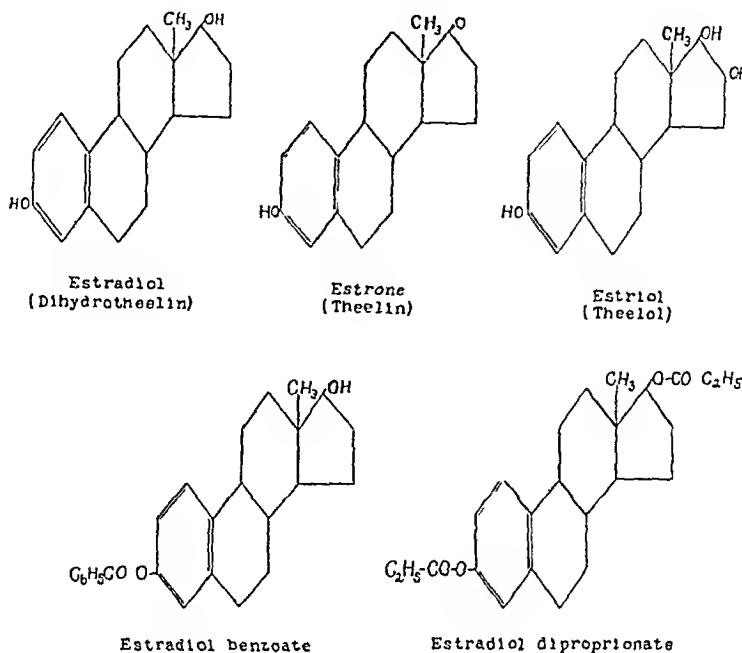
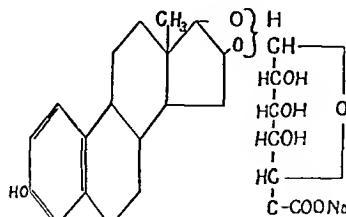


Figure 2

have been effected *in vitro* and demonstrated *in vivo*. Estradiol (dihydrotheelin) is the only one which has been actually isolated from ovarian tissue, as I stated earlier, and the activity of the follicular fluid is in a large measure accounted for by the estradiol content. The remaining fraction is ketonic in nature and is probably estrone. Estrone and estriol have been isolated from the urine of normal and pregnant women and from certain tissues of the body. These findings, in themselves, indicate that estrone and estriol may be the metabolites of estradiol. Further evidence supporting this view was furnished by Westerfeld and Doisy<sup>19</sup> and by Pincus and Zahl<sup>20</sup>. They demonstrated the *in vivo* conversion of the hormones after injections into rabbits and monkeys.

The site of conversion or metabolism of the estrogen in the body is still uncertain. Pincus and Zahl claim that the conversion of estrone to estriol in the rabbit requires a functional uterus, for they could not demonstrate this conversion in hysterectomized or long-time castrated animals. Westerfeld and Doisy,<sup>19</sup> however, found that the presence or absence of the uterus had no effect on the conversion of estradiol to estrone and vice versa. Whether or not these two sets of experiments deal with two different mechanisms is not yet known.



Estriol glucuronide

Figure 3

The urinary estrogens are largely excreted in a combined form, as is indicated by the discovery that yields of estrogen from urine are markedly increased by preliminary hydrolysis Marrian and co-workers<sup>21</sup> have isolated the combined estriol from human pregnancy urine and found it to consist of estriol glucuronide, the linkage involving the terminal aldehyde group of the glucuronic acid and the hydroxyl group of carbon 16 or 17 of the estriol The complete explanation for this conjugation is not yet known However, it is well known that glucuronic acid is used by the organism in detoxicating many substances Also, the conjugation with glucuronic acid increases the water solubility of estriol A third fact, demonstrated by Marrian<sup>22</sup> is that the glucuronide is relatively inactive as compared with the free estriol Thus it may be that the conjugation is made by the organism in order to detoxicate the estriol, to increase its solubility in the urine or to inactivate the estrogenic potency or for all three reasons That the inactivation may be of particular importance during pregnancy is suggested by Marrian's finding that shortly before the onset of labor the proportion of free estrogen rises very markedly Marrian deduced from this that possibly the increase in free estrogen is for the purpose of sensitizing the uterus to the oxytocic principle of the pituitary and so to facilitate the onset of labor During the first eight and one-half months of pregnancy there is no need for sensitization of the uterus to oxytocin and so the estriol is converted to the relatively inactive glucuronide

Estrone is also conjugated before excretion Preliminary work by Schacter and Marrian<sup>23</sup> suggests that in pregnant mares' urine, estrone is present in combination with sulphuric acid Whether or not this is also true for the estrone of human pregnancy urine is not yet known

The nature of the estrogen conjugates of normal human urine is likewise unknown

The site in the body where the estrogens are conjugated and so rendered inactive appears to be the liver. Zondek,<sup>24</sup> a number of years ago, showed that estrogen was inactivated when incubated *in vitro* with liver. Israel and his colleagues<sup>25</sup> found inactivation to occur in a lung-heart-liver perfusion system, but not in a lung-heart preparation. Golden and E. L. Sevrinckhaus<sup>26</sup> noted that in animals in which the ovaries were transplanted into the mesentery no evidence of heat appeared, and Biskind and Mark<sup>27</sup> showed that pellets of estrone implanted in the spleen when the circulation was intact gave no response, whereas if the splenic artery and vein were ligated the pellets were effective, presumably because of absorption by the non-portal part of the circulation. Although a role of the altered spleen cannot be overlooked in the inactivation of the estrone in these last experiments, nevertheless the evidence from these various experimental approaches seems definitely to show that the conjugation and consequent inactivation of the estrogens takes place in the liver. If an estrogen is always destroyed in its passage through the circulation of the liver, however, it is puzzling to understand how this substance, when given by mouth, can be effective. Estriol, it will be recalled, is quite effective by mouth in experimental animals, at least. Another puzzling finding is that of Dingemanse et al.,<sup>28</sup> who have recently reported that considerable amounts of combined estrogen are found in ovaries. It seems quite unlikely that this could have been conjugated in the liver and then stored in the ovaries, although this is a possibility. If such is not the case the alternative remains of it having been actually secreted in the ovary in a combined inactive form.

The inactivation of estrogen by an organ such as the liver may partially explain the pronounced response from percutaneous or per-epithelial administration, even though the rate of absorption is low, for in this method of administration all the estrogen would act on the underlying structures before passing into the circulation and there being inactivated in its passage through the liver circulation.

The active substance peculiar to the corpus luteum, named progesterone, was isolated in 1934, simultaneously by four different laboratories. Its structure has been determined, showing it to belong to the same family of compounds as the estrogens. It is to be noted that progesterone has quite different active groupings from the estrogens (Figure

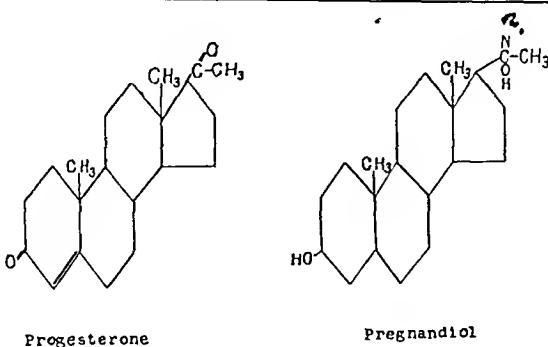


Figure 4

4) Instead of a phenolic hydroxyl on carbon 3, progesterone has a ketone group with a single unsaturated linkage in this position. On carbon 17, instead of a hydroxyl or ketone group, progesterone has an acetyl group. In addition, progesterone has the usual sterol methyl group on carbon 10. This, it will be recalled, is absent in the estrogens.

It is converted by the endometrium, according to Venning and Browne,<sup>29</sup> into an inactive compound, pregnandiol. These investigators report that during pregnancy and during the last half of the menstrual cycle, when luteal activity is high, pregnandiol is excreted in the urine. Similarly they find that injections of progesterone into ovariectomized women, previously sensitized by estrogen, result in pregnandiol excretion. However, no pregnandiol could be demonstrated after administration of progesterone into hysterectomized women. This led Venning and Browne<sup>29</sup> to postulate that the reduction to pregnandiol takes place in the endometrium. However, recent work by Buxton and Westphal<sup>30</sup> indicates that other mechanisms for the conversion are possible. They find that normal and pathological men, treated with progesterone, excrete almost theoretical amounts of pregnandiol. In these cases, certainly, the conversion could not take place in the uterine endometrium.

Venning and Browne have advocated the use of urinary pregnadiol determination as a measure of corpus luteum activity. That the determination has a great value is undeniable. However, it should be remembered that the pregnadiol is but the end product of the chemical reduction of progesterone. A large number of intermediate products is possible—in fact, many of them have been isolated from urine. It therefore appears that negative findings as to pregnadiol excretion need not necessarily mean lack of luteal activity. It is quite possible that pro-

gesterone may be secreted at a normal rate by the corpus luteum but that its conversion to pregnandiol is incomplete. Thus, one would find little of this compound in the urine, although a careful search might show the presence of other degradation products of progesterone. It is evident that in order to determine the presence or absence of active corpora lutea, pregnandiol determinations should be supplemented by uterine biopsies.

### THE ACTION OF ESTROGEN

The estrogens are powerful pharmacological agents. A response of the female accessory reproductive organs was the first one noted and is the most prominent effect and so it is quite logical that it has been the one on which attention has been primarily focused, and effects on other structures neglected. The few studies which have been made on other responses make it unsafe to assume, however, that only the reproductive system, including the mammary gland, is affected by these hormones. These remarks could be justified even though no relationship to the genesis of cancer had been established. The reaction induced by the various estrogens is similar, differing only in intensity and duration, and so can here be treated as due to a single substance.

The action of estrogen on the uterus is well known and need be only briefly discussed. The uterus after ovariectomy undergoes profound involution, the glands become short and few in number and the epithelium of a low non-secretory type. If estrogen is administered all parts of the organ are stimulated. The myometrium becomes thicker and more vascular. The endometrium particularly responds, becoming thickened and showing a growth in the number and length of its glands, and some glycogen deposition takes place in the basal zone of the gland cells. The epithelium is increased in height. The vascular response is immediate, pronounced and striking, as shown by direct observation of the uterus in rabbits through an abdominal window and of endometrial transplants in the anterior chamber of the eye (Markee,<sup>31</sup> Pompen<sup>32</sup>). There is an early increase in the acetylcholine content, as shown by the fact that atropine will inhibit the dilatation of the vascular bed and by tests on eserized frog muscle (Pompen,<sup>32</sup> Reynolds<sup>33</sup>). The endometrium imbibes fluid from the dilated and slowed circulation. These vascular changes precede the later enhanced growth and metabolic changes. The resultant effect is then a proliferation of epithelial cells and a thick-

ened and a highly vascular and edematous endometrium. For the development of the type of endometrium in which implantation of the fertilized egg can take place, the second female sex hormone, progesterone, is necessary. Although its first action, as shown by experimental work, is to increase mitoses in the glands and epithelial lining of the uterus (Lloyd<sup>34</sup>), its later and specific effect is to bring about a secretory condition in this epithelium. Glycogen, which lies in the basal portion of the gland cells in the estrogen phase, is transferred to the apical zone and together with mucus is secreted into the lumina of the glands. The lumina become not only filled with this secretion but become enlarged and irregular in shape.

Although the induction of this secretory or progravid state of the endometrium is a specific action of the corpus luteum hormone, its action is enhanced by estrogen, that is, the amount of progesterone necessary to produce a progravid endometrium is decreased by injecting estrogen (Hisaw et al.<sup>35</sup>) Engle and Smith<sup>36</sup> \* Not only is the progesterone response enhanced by estrogen, but, as has been experimentally shown, the progravid condition can be maintained for a longer period if estrogen is concurrently administered. This work, which has shown that the progesterone response is enhanced by estrogen, thus correlates with what I have described earlier, namely, that the corpus luteum normally secretes both progesterone and estrogen.

\* In earlier work (Hisaw and Leonard<sup>37</sup> Cluberg<sup>38</sup> Robson<sup>39</sup>) on the combined action of estrogen and progesterone on the endometrium of rabbits, it was found that the progestational effect of progesterone was nullified by the concurrent injection of relatively small amounts of estrogen. Estrogen is pronouncedly antagonistic to progesterone in rabbits and the progestational action of the latter is nullified if about 1/75 to 1/100 of its weight of estrone is administered, or in international units, a ratio of about 1 to 100. However, even in rabbits the addition of some estrone to the progesterone after a progravid condition had been developed by progesterone alone, prolongs the progravid condition (W. M. Allen<sup>40</sup>). Normally the progravid condition induced by progesterone administration in spayed rabbits disappears by the tenth day. In order to secure a progesterone response it is necessary, of course, to sensitize the uterus by a preceding series of estrogen injections.

In monkeys the estrogen-progesterone ratio which will prevent the progestational reaction is much higher than in rabbits. A daily dosage of estrogen as high as 500 R.U. or approximately 2500 to 5000 I.U. does not inhibit the action of 5 I.U. of progesterone, a ratio in I.U. of 5000-10,000 to 1 (Allen, Hisaw and Gardner<sup>41</sup>). These findings in monkeys appear to correlate much better with those in the human than does the work on rabbits, although no precise experiments have been reported in the human. Not only is it well known that corpora lutea in the human contain much estrogen, but in addition assays of blood and urine show a much larger amount of estrogen than can be found in lower forms, including monkeys. It seems safe to assume that the action of the progesterone from the human ovary is increased and not inhibited in the human by the circulating estrogen.

I would like to point out, however, that the response of the endometrium does not depend solely on the action of estrogen and progesterone, but is influenced by altered body states. In hypophysectomized monkeys we have found that the response to these hormones is less than in spayed animals and that the latent period between withdrawal of both estrogen and of progesterone and menstruation is very greatly increased. The cachexia and other disturbances induced by hypophysectomy evidently reduce the quantitative responses to these hormones, although qualitatively their actions are not changed.

Curious as it may seem, work has established that estrogen assists in the structural and presumably the functional maintenance of the corpus luteum itself. I refer to the work of Westman<sup>42</sup> and of Robson<sup>43</sup> in rabbits in which it was shown that the rapid regression of the corpora which characteristically occurs after hypophysectomy can be prevented by the administration of estrogen. In such an experiment it is obvious that this maintenance cannot be indirectly due to a stimulation of the hypophysis. Although an indirect effect through other endocrine glands has not been disproven, nevertheless this work indicates that estrogen, an ovarian secretion, assists in the maintenance of an ovarian structure, the corpus luteum. This could justifiably be characterized as a gonadotropic effect of estrogen. This corpus luteum maintenance effect of estrogen, however, is not permanent and regression of the corpora ultimately occurs, even though the injection of estrogen is continued. Regression which would normally occur within five days is postponed only until the thirteenth to the sixteenth day, which is the period that corpora lutea remain functional in pseudopregnancy in rabbits. We have to admit that the reactions of the reproductive organs of rabbits are peculiar in some respects and that this gonadotropic effect of estrogen may not hold in monkeys and the human. The presumption is, however, that the same response will be found in these higher forms.

It seems desirable to mention some of the hormonal conditions obtaining in pregnancy, for not only is the maintenance of the state of pregnancy dependent on the continued secretion of the ovaries in most forms, but the newly formed organ, the placenta, is a secretory organ and supplies hormones normally secreted primarily by the ovary. In most laboratory animals abortion soon takes place, when the ovaries are removed. Such is not the case in the human, in monkeys, in guinea pigs and in mares. Except in monkeys, the literature is sufficiently extensive

and definite to establish that the ovaries are not essential for the continuation of pregnancy in these species

A number of years ago Robert Frank pointed out that the placenta probably had a secretory function, and this has been found to be the case. It appears to be highly probable, and indeed established, that the gonadotropic hormone which appears in the urine in large amounts early in pregnancy in women is formed by the placenta. The designation of this hormone as chorionic gonadotropin is being widely adopted and this name was accepted at the Third International Conference on the Standardization of Hormones held in Geneva last year. Estrogen continues to be present after the removal of the ovaries during pregnancy, although further studies are desirable to determine if it is in normal amounts and how great a reduction invariably occurs after ovariectomy. The placenta contains a higher concentration of estrogen, mostly as estriol, than any other organ of the body.

Less work has been done on the placental source of progesterone than is the case with the estrogens. A method for the assay on the excreted degradation products of progesterone has only recently been devised, and though it has already proven of great value in supplying additional evidence on the period when progesterone is secreted in the normal cycle and during pregnancy, nevertheless but little work on the effect of ovariectomy on the secretion of progesterone in pregnant women has been done. Browne et al<sup>44</sup> and Jones and Weil<sup>45</sup> have reported pregnandiol excretion after excision of the corpus luteum during pregnancy. In the case of Jones and Weil there was a temporary drop followed by a return to nearly normal levels. Even though data do not conclusively show that the placenta secretes estrogen and progesterone, it appears highly probable that such is the case and that in the special condition of pregnancy the placenta supplements and indeed can take over in the human the secretion of the female sex hormones in the absence of the ovaries.

I shall not include a discussion of the effects of estrogen and progesterone on the two other main structures of the reproductive system, the vagina and mammary glands. Proliferation of the epithelial elements of both organs is caused by estrogen. In the vagina there is an increased deposition of glycogen and a consequent lowering of the pH. This increased acidity and accompanying epithelial proliferation and cornification is probably responsible for the benefit in gonorrhreal vaginitis.

As stated earlier in the paper, the extra-reproductive effects of estrogen have not been investigated nearly as extensively as have the responses of the reproductive organs. Studies, it is true, have been made on such subjects as the influence of estrogen on ketosis, carbohydrate, fat and basal metabolism, serum calcium, and blood formation, but not only is more work required before significant or at least definite conclusions, in most cases, can be drawn, but also any indirect effect through the pituitary gland must be further tested, so that it would be premature to attempt to draw conclusions at this time.

Although blood pressure determinations after estrogen injections are negative and consequently an effect on the larger blood vessels and the heart is improbable, nevertheless significant and definite changes have been reported in the peripheral circulation. Work on the peripheral vessels was stimulated from two findings. First, injection of estrogen causes within an hour in rabbits a pronounced hyperemia. This is not due to a heightened metabolism of the tissue, for the hyperemia precedes an increase in oxygen consumption. Secondly, the hyperemia from estrogen injection is not limited to the uterus but is participated in by the sexual skin in monkeys and by the nasal mucosa. The hyperemia persists throughout the estrogen injection and leads at least in the uterus and the sexual skin of monkeys to water retention and a high osmotic pressure of the interstitial fluid (Aykroyd and Zuckerman<sup>46</sup>) and sodium retention (Thorn and Harrop<sup>47</sup>). In a form in which the sexual skin changes are pronounced, the water retention is sufficient to produce a significant increase in body weight (Krohn and Zuckerman<sup>48</sup>). The weight increase is accompanied by a decrease in urine output. Although a change in the water content of the skin is more pronounced in forms having a distinct swelling of the sexual skin, nevertheless an effect on water retention from estrogen injections has also been shown to occur in rats, a species in which there is no external manifestation of changes in the skin (Zuckerman et al<sup>49</sup>). This shift in water to the skin in rats amounts to almost 1 per cent of the body weight and is accompanied by slight decrease in the water content of muscle and certain of the organs. This water retention effect of estrogen is also induced by other sterol hormones, although certain differences, as in nitrogen retention, occur and Zuckerman<sup>50</sup> states that the excretion of water which has accumulated in the sex skin of monkeys from estrogen administration is not prevented by progesterone, testosterone or cortin. The effect of estrogen

on the peripheral circulation has been further explored by Reynolds and his co-workers in rabbits and the human. By direct observation on the transilluminated ear of rabbits Reynolds and Foster<sup>51, 52</sup> observed that injection of estrogen caused a dilatation of the capillaries and small venules. The ear became pink. That there was usually not an increased blood flow was evidenced by a fall rather than a rise in the temperature of the ear. The effect was limited solely to the small peripheral vessels as there was no constant change in blood pressure. In measurement of the volume of the finger in men they (Reynolds and Foster<sup>53</sup>) found an increase which averaged 4.6 per cent in twelve subjects, whereas in six there was no response. Although the increase was small, attention was called to the fact that the fleshy part of a finger comprises only about one-half the total volume of this digit, and an increase in size would be limited to the soft part and not to the hard part—the nail and bone. Although work on the peripheral vascular responses has not been extensive, yet sufficient work appears to have been done to establish that vascular effects are not limited to the sexual organs of the female.

The mechanism by which estrogen alters the peripheral vascular bed, so far as it has been elucidated, seems to be an interesting one. Pompen<sup>32</sup> found that the heightened vascularity of the uterus induced by estrogen injections would be inhibited by atropine sulphate. This indicated that the response might be due to an increase in acetylcholine. Reynolds<sup>51</sup> has carried out a series of assays of the acetylcholine content of the uterus. He finds that in ovariectomized rabbits no trace of this substance could be found in most cases, whereas within an hour after an injection of an estrogen (Amniotin, Squibb) a very appreciable amount was present. Whether, in the general peripheral vascular bed, acetylcholine is the agent responsible for the dilatation of the small vessels remains yet to be established. That such may be the case is indicated by the interesting findings reported by Soskin and Bernheimer<sup>54</sup> in atrophic rhinitis. These investigators postulated that the beneficial effects in atrophic rhinitis reported by Mortimer et al<sup>55</sup> and by Blaisdell,<sup>56</sup> from injections of estrogen, were due to hyperemia. They tested this hypothesis not by local application of acetylcholine, which might be dangerous, but by potentiating that which was normally present but which is inactivated by choline esterase. They inhibited the action of the latter with local applications of a physostigmin-like substance. In a moderate-sized series, fourteen patients, this treatment, they report, gave better

results than were secured with local applications of estrogen. If further work confirms this report, it will be an excellent example of an immediate practical application of findings which appeared to be of theoretical physiological interest only.

Among the extragonadal effects of estrogen the action on the anterior pituitary gland is outstanding. This action is so well known, however, that a brief discussion will suffice.

It was early noted that the daily subcutaneous injection of estrogenic preparations damaged the reproductive apparatus of male animals. At first this was attributed to a hormone antagonism but when it was later found that ovarian atrophy also resulted, it seemed likely that the injury was due to decreased hypophyseal activity. This view was strengthened by the discovery that the injection of gonadotrophic hormone concurrently with estrogen prevented the ovarian atrophy in normal animals and that in hypophysectomized rats estrogen administration did not decrease the effect of gonadotrophic hormones. The physiological evidence seemed to show clearly a depressant effect on the hypophysis. Evidence soon appeared, however, showing in certain but not in all forms that estrogen caused a formation of corpora lutea, a finding which would indicate an enhanced output of luteinizing hormone, according to the ideas current about the two hypophyseal gonadotrophic hormones. There was thus suggested a reciprocal relationship between the ovaries and the hypophysis, which would very nicely explain the rhythmicality of the female sex cycle. With the growth of the follicles in the first half of the cycle there would be increasing secretion of estrogen which in turn would depress the output of follicle-stimulating hormone and increase the secretion of luteinizing hormone. As the correct balance between these two gonadotrophic hormones was reached, rupture of the follicles would result and corpora lutea would form and be maintained by the luteinizing hormone. Such a concept, as shown by subsequent work, is far too simple. Luteinizing A P hormone, as prepared by present methods, does not maintain the corpora lutea, but rather in some forms, at least, it causes their disappearance. The lactogenic hormone, on the other hand, induces the functional and structural persistence of the corpora lutea. The ovarian-hypophyseal interrelationship in the cycle is apparently not as simple as was outlined. The marshalling of additional data frequently spoils these simple *schemata*.

However, both experimental and clinical work show that estrogen,

when given in considerable amounts, represses the liberation of at least one of the two or more gonadotropic hormones supposed to be secreted by the hypophysis. Even this finding, which seems clear from all physiological evidence, is difficult, however, to harmonize with the structural changes which occur in the hypophysis, for these changes definitely indicate an increased activity of the basophiles. However, it is certain that the administration of estrogen decreases the urinary output of pituitary gonadotropic hormone which normally rises at the menopause, a rise which has been given as the cause of the menopausal disturbances. This may well be too simple an explanation, for the influence of estrogen is not limited to the hypophysis and the reproductive system as pointed out earlier in this paper.

The repressing effect of estrogen on the hypophysis is not limited to the gonadotropic hormone or hormones. A number of experimental studies have shown a slowing or indeed a stoppage of the growth in young animals. Although there are differences of interpretation in regard to the changes in the epiphyseal cartilages from estrogen administration (Tusik and de Fremery,<sup>57</sup> Zondek,<sup>58</sup> Pfeiffer and Gardner,<sup>59</sup> Silberberg and Silberberg<sup>60</sup>), it can be stated that, whatever may be the nature of these changes, it is certain an abrupt stoppage of growth can be induced in experimental animals (Deanesly<sup>61</sup> and others). The injection of estrogen, however, could hardly be recommended as a method for limiting growth in the human, because the effects of this hormone are general, as I have emphasized earlier in this paper. In addition to the depressant effects on growth, we can add the more questionable one of depression of the thyroid and the induction of an adrenal hypertrophy.

In this paper I have limited myself to a discussion of the action of the ovarian hormones, for this subject is sufficiently complex to make me well-satisfied to have had the pituitary gonadotropic hormones and their action on the ovaries discussed earlier in the Fortnight series by J. B. Collip. I may, perhaps, have appeared to overemphasize the complexity of the action of estrogenic hormones, although I believe such is not the case. I have tried to point out that the estrogens—certainly much more so than progesterone—are powerful pharmacological agents. Even though we overlook the possibility of carcinogenic effects, they cannot be given with assurance that their action will be circumscribed or limited. The advance in our knowledge about the action of the female sex hormone has been rapid, for it is only in the last few years that these substances

have been made available in quantities sufficient to carry on adequately experimental and clinical investigation with them. Since these hormones are powerful pharmacological agents and have a widespread action on the body, it is important to keep in mind that they should not be promiscuously given and that it is important to know when they should not be used as well as to know when they may be of value.

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# THE BIOLOGICAL SIGNIFICANCE OF NICOTINIC ACID

*Harvey Lecture, November 16, 1939*

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For we review briefly the developments in the field of biochemistry, we find that chemical elements and chemical compounds have become biologically significant by diverse pathways. The various methods by which the five recognized members of the B complex have come to be known as specific chemical compounds makes an interesting story in itself. In the case of riboflavin the new compound was isolated and later associated with fundamental processes in the living cell. In the other cases the necessity of compounds of specific character was recognized first and finally the actual compounds were isolated and identified. Thiamin, vitamin B<sub>6</sub>, and pantothenic acid turned out to be compounds of rather unique structure, quite different from those generally found in living matter. On the other hand, the antpellagra factor was found to be a compound which had been known for many years.

It is quite obvious that in all cases our knowledge of the biological significance of these factors has increased more rapidly after the compounds became available in pure form. Thus we are not so interested in the manner in which the significance was recognized as we are in the entire and complete picture. It is my purpose this evening to give you as complete a picture as I can of the facts concerning the third member of the vitamin B complex—nicotinic acid.

Huber<sup>1</sup> first prepared nicotinic acid in 1867 by the oxidation of nicotine. Its isolation from biological material was not achieved until 45 years later when Funk<sup>2</sup> isolated nicotinic acid in crystalline form from yeast concentrates which possessed antineuritic activity. The acid itself, however, displayed no activity in curing pigeon beriberi. At about the same time Suzuki, Shimamura, and Odake<sup>3</sup> isolated nicotinic acid from rice polishings. In 1916 Willmaris<sup>4</sup> impressed by the common occurrence

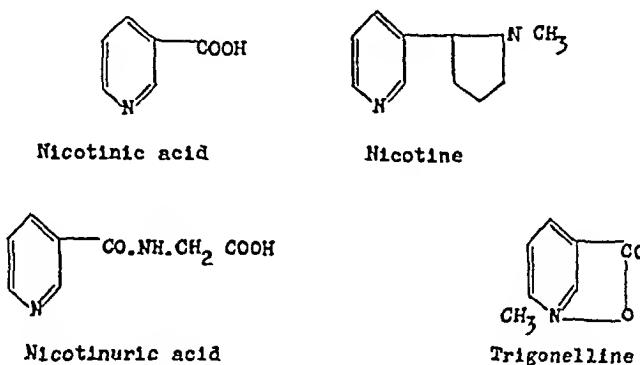


Figure 1

of nicotinic acid with the antineuritic vitamin in several natural substances, again tried nicotinic acid, trigonelline, as well as other pyridine derivatives for antineuritic potency, but none of them caused any permanent improvement in polyneuritic fowls. Trigonelline, the methyl betaine of nicotinic acid, was isolated from plant material by Jahns<sup>5</sup> in 1885. In 1912 Ackermann<sup>6</sup> found that dogs given fairly large amounts of nicotinic acid excreted in the urine about equal amounts of trigonelline and nicotinuric acid (the dipeptide of nicotinic acid and glycine). The formulæ for these compounds are given in Fig. 1.

Except for the work of Szymanska and Funk<sup>7</sup> who attributed an appetite-stimulating and weight-preserving action to nicotinic acid and the amide, very little interest was shown in the possible role of pyridine derivatives in living systems until the work of Warburg and Euler in 1935. Warburg and Christian<sup>8</sup> characterized nicotinic acid amide as one of the hydrolysis products from the coenzyme which they had isolated from blood and which is now known as coenzyme II. Kuhn and Vetter<sup>9</sup> isolated nicotinic acid amide from heart muscle and Euler, Albers, and Schlenk<sup>10</sup> from cozymase.

This work gave new impetus to the application of these compounds in the field of nutrition. Euler and Malmberg,<sup>11</sup> using a diet similar to the Sherman-Bourquin diet supplemented with vitamin B<sub>1</sub> and riboflavin, found no growth response with the acid or amide although the rats receiving the acid lived longer. Funk and Funk<sup>12</sup> found larger food intake and better growth in rats and pigeons on certain rations when given the acid and especially the amide. In our own laboratory<sup>13</sup> we observed a growth stimulus from nicotinic acid when fed with adenylic

acid to rats on a factor W deficient diet. However, none of these responses was of sufficient magnitude to attribute to nicotinic acid real vitamin-like properties.

Let us now turn our attention to the human disease, pellagra. Almost twenty years ago Dr. Voegtlin presented before this Society the studies on pellagra available at that time and concluded that the disease could be prevented by appropriate diet, but the nature of the dietary factor had not been discovered. By 1930, due to the excellent work of Goldberger and co-workers, pellagra had been definitely established as a deficiency disease and the protective factor was associated with the more heat stable fraction of the B complex which had been distinguished from vitamin B<sub>1</sub> by animal experimentation. A pellagra-like condition had been produced in rats on diets low in the B complex supplemented with an alcoholic extract of corn. I want to emphasize at this time that Goldberger never referred to this syndrome as anything except a pellagra-like condition. The symptoms observed in rats by Goldberger were undoubtedly those which we associate today with vitamin B<sub>6</sub> and riboflavin deficiency. Considerable difficulty was encountered in producing this condition consistently but the growth-stimulating effect of various foods when added to this diet continued to be used as a measure of antipellagra activity. All the values in the literature were based on these assays except the limited figures reported by Sebrell<sup>14</sup> from studies with dogs.

In 1930 the value of liver extract in the treatment of pellagra in humans as well as its activity in the prevention of vitamin B<sub>2</sub> deficiency in rats was recognized. Goldberger and Sebrell<sup>15</sup> found liver extract 343 to be a good source of the factor necessary for the prevention of black tongue in dogs. Spies<sup>16</sup> and Smith and Ruffin<sup>17</sup> found that fairly large amounts of liver extract by mouth were efficacious in treating pellagra. At about the same time I was working in the Biochemical Laboratory, Cambridge, England, and Dr. Guha, who was also working there, found the liver extract, which I had brought along for another purpose, produced excellent growth in rats on a vitamin B<sub>2</sub> deficient diet. The following year Salmon and Guerrant<sup>18</sup> found liver extract to be four times as rich in vitamin B (B<sub>2</sub>) as a sample of brewers' yeast. We now know that the growth obtained in both cases must have been due mainly to the riboflavin present in the liver extract. However, the above results were sufficient to convince me that liver extract might be an excellent material for the isolation of the antipellagra factor.

Attempts in our laboratory to produce pellagra-like lesions in rats failed completely and we turned our attention to chicks. A pellagra-like condition was produced in the chick by feeding a heated natural grain ration, and the assays of our fractions from liver extract depended upon the prevention of these lesions. We<sup>19</sup> soon had the first indication that the factor active in this syndrome was separate from riboflavin which Kuhn, Gyorgy, and Wagner-Jauregg<sup>20</sup> had just isolated and shown to have growth-promoting properties in rats. Concentrates of riboflavin were completely inactive for the chick while purified fractions from liver retained their potency after removal of riboflavin. Lepkovsky and Jukes<sup>21</sup> soon confirmed our experimental results and introduced the name "filtrate factor" for the active substance in the filtrate after removal of the riboflavin with fuller's earth. This designation did not exactly please us since naturally we felt that we were dealing with the true antpellagra factor, but both Dr. Lepkovsky and I recognized that there was no evidence available to show that the pellagra-like condition in chicks was identical with human pellagra. It was therefore necessary for us to repeat our work using dogs, since most authorities agreed that black tongue in dogs was identical with human pellagra. Again<sup>22</sup> riboflavin had no effect on black tongue while the purified concentrates free of riboflavin were highly active in curing this syndrome. Birch, Gyorgy and Harris<sup>23</sup> confirmed the fact that riboflavin had no curative action in dogs and Dann,<sup>24</sup> Spies,<sup>25</sup> and Fouts, Lepkovsky, Helmer, and Jukes<sup>26</sup> reported complete inactivity of riboflavin in the treatment of human pellagra.

Further purification of the liver fractions gave concentrates which contained very small amounts of solid material and which were highly active in both chicks and dogs. It was not surprising that we believed that the chick and dog required the same factor. Within a very short period we<sup>27</sup> demonstrated the activity of nicotinic acid in the cure of black tongue, and isolated nicotinic acid amide from liver extract concentrates. The activity of nicotinic acid in the treatment of black tongue was soon verified by Street and Cowgill,<sup>28</sup> Dann,<sup>29</sup> and Sebrell and co-workers<sup>30</sup>. However, when we<sup>31</sup> tried nicotinic acid or the amide on chicks we found these compounds completely inactive in the prevention of the pellagra-like lesions in this species. The chicks had provided a means of assay not because we were actually testing for nicotinic acid but because we were testing for the chick antidermatitis factor which followed the nicotinic acid amide very closely. Recent work in our

laboratory conducted by Dr. Woolley has identified the chick anti-dermatitis factor as pantothenic acid.

The activity of nicotinic acid in the treatment of black tongue suggested its therapeutic use in human pellagra and its successful use has been reported by a number of workers in the field. The value of nicotinic acid has recently been reviewed by Spies, Bean, and Ashe<sup>32</sup>. They make the following summary concerning its use: "In cases of acute or chronic pellagra in relapse it will (a) cause fading of the fiery red lesions of the mucous membranes and diminish the Vincent's infection associated with it, (b) in most cases, restore to normal disturbed gastrointestinal function, (c) restore to normal the mental function deranged moderately or severely in acute pellagra, (d) cause fading of the dermal erythema but not cure chronic changes of the skin. In cases of sub-clinical pellagra, the vague ill-defined symptoms disappear and in persons subject to recurrences of the disease the development of clinical pellagra is prevented. In both clinical and subclinical pellagra, the sense of well-being, one of the attributes of health, is restored."

Very recently Cleckley, Sydenstricker, and Geeslin<sup>33</sup> have reported the beneficial effect of nicotinic acid in the treatment of atypical psychotic states.

Katzenellenbogen<sup>34</sup> working in Palestine brought about considerable improvement in twenty-one out of twenty-four cases of stomatoglossitis, characterized by soreness of the tongue and angles of the mouth and sore throat. Landor,<sup>35</sup> however, could not cure stomatitis with nicotinic acid but did find yeast to be active. It is quite possible that these conditions may be related to the cheilosis which Sebrell<sup>36</sup> has shown to be due to a riboflavin deficiency.

Nicotinic acid has also been used in the treatment of disorders related to black tongue in dogs and certain intestinal disturbances in pigs. It is safe therefore to conclude that diets low in nicotinic acid or compounds which yield nicotinic acid on ingestion allow the development of pellagra and related disturbances in humans and similar conditions in dogs, pigs and monkeys.

The above results raise certain pertinent questions: (a) What is the distribution of nicotinic acid or nicotinic acid precursors in natural foods? (b) Are other compounds equally as effective as nicotinic acid, and (c) How does nicotinic acid function in the animal body?

The successful use of natural foods as a source of this vitamin de-

pends upon the availability of complete figures for its distribution in a large variety of foods Possible methods for determining the distribution of nicotinic acid include chemical procedures, bacterial growth methods, and animal assays The method of Karrer and Keller<sup>37</sup> based on the color produced with 2,4 dinitrochlorbenzene is definitely not reliable since the value given by Karrer for liver is one-tenth of the amount of nicotinic acid amide which we actually isolated from liver and we calculated that we recovered only one-twentieth of that present The method which has been most satisfactory depends upon the breakdown of the pyridine nucleus by cyanogen bromide and aniline to give a yellow colored compound which can be measured colorimetrically Swaminathan<sup>38</sup> has used this method on foods and Shaw and Mac- Donald<sup>39</sup> on commercial liver extracts Bandier and Hald<sup>40</sup> have used p-methylaminophenol in place of aniline, and Bandier<sup>41</sup> has recently applied this method to biological material with satisfactory results

Nicotinic acid was shown to be an important growth factor for *Staphylococcus aureus* by Knight,<sup>42</sup> for diphtheria bacillus by Mueller,<sup>43</sup> and for dysentery bacillus by Koser, Dorfman, and Saunders<sup>44</sup> Although some of these methods have been used for the quantitative estimation of nicotinic acid in body fluids, no extensive studies have been made on foods Similarly cozymase has been determined through the use of the bacilli of the *influenzæ* group as originally demonstrated by Lwoff and Lwoff but as yet this method has been applied mainly to blood by Vilter, Vilter, and Spies<sup>45</sup> and by Kohn<sup>46</sup>

As far as animal assays are concerned, both the rat and the chick are eliminated at least for the time being We have, therefore, continued to rely upon the dog for our assays The curative method has been used almost exclusively Black tongue was produced on our regular basal ration containing

Yellow corn	72
Purified casein	18
Cottonseed oil	5
Cod liver oil	2
$\text{Ca}_2(\text{PO}_4)_2$	1
$\text{CaCO}_3$	1
$\text{NaCl}$	1
Thiamin	50 gamma per K per day
Riboflavin	" " " " "

TABLE I

## NICOTINIC ACID POTENCY OF FOODS BASED ON BIOASSAYS WITH DOGS

Material	Mg per gm dry weight	Material	Mg per gm dry weight
Liver, pork	1.2	Tongue, beef	0.4-0.5
Liver, lamb	1.2	Veal	0.5
Liver, veal	0.9	Brain, beef	0.3-0.5
Kidney, pork	0.85-1.0	Heart, pork	0.3
Yeast, brewers	1.0	Heart, beef	0.3
Yeast, bakers	0.5	Dried cereal grasses	0.1-0.15
Pork, loin	0.45-0.6	Skim milk powder	0.5-1.5
Pork, ham	0.4	Wheat germ	0.5-1

The response of each dog to standard amounts of nicotinic acid was determined before any assays were started and again after two or three assays had been made. The response measured was that obtained from a single dose of food material, all of which was consumed within a period of 24 hours.

Table I summarizes some of our results calculated as milligrams of nicotinic acid per gram of dry food. Our results are somewhat higher than those given by Bandier. It is entirely possible that the response shown by dogs when given liver as a source of nicotinic acid is somewhat greater than that resulting from nicotinic acid alone, but we must not overlook the possibility of incomplete extraction in the chemical procedures. If we assume the daily human requirement for nicotinic acid is 25 mg, then 25 gm of dry liver or one-quarter of a pound of fresh liver will supply the requirement. About one-half pound of lean meat per day will amply meet the need.

In the assay work it became apparent immediately that only certain foods will produce rapid improvement when given at levels which will be consumed readily by the sick dog. This group includes practically all animal tissues and yeast. Foods like wheat germ and skim milk gave a response only when the supplements were continued over a period of several days. The availability of a reliable chemical method will greatly facilitate the work on the distribution of this vitamin in foods. In gen-

TABLE II

## ANTI-BIACK TONGUE ACTIVITY OF VARIOUS PYRIDINE DERIVATIVES

Active	Inactive
Nicotinic acid	Pyridine
Nicotinic acid amide	Picolinic acid
Ethyl nicotinate	Isomicotinic acid
Nicotinic acid N methyl amide	Nipeptic acid
Nicotinic acid N diethyl amide	6-Methyl nicotinic acid
$\beta$ -Picoline	Trigonelline
Nicotinuric acid	1-Methyl nicotinic acid chloride
	Quinolinic acid
	$\beta$ -Aminopyridine

eral we may say that most natural foods will vary from 1 to 100 mg of nicotinic acid per 100 gm dry material. Certain crude liver extracts may contain as high as 200 to 300 milligrams per 100 grams. In order to supply amounts of nicotinic acid which have proved effective in the treatment of pellagra, it would be necessary to feed at least 100 grams of the more concentrated sources.

As long as severe pellagra is encountered, I imagine the use of nicotinic acid or related compounds will have to be continued, but when it is used we must remember that there are at least five other members of the B complex which may also be low in the diet of pellagrins. Work both in the field and with dogs on the Goldberger diet indicates a possible deficiency of thiamin and riboflavin.

Dogs grow very well on the Goldberger diet supplemented with thiamin, riboflavin and nicotinic acid, but if the corn in such a diet is replaced by sucrose the dogs will grow for only a short time and then begin to lose weight. The addition of 2 per cent of liver extract renders the diet complete. We are still working on the fractionation of liver extract, but to date we are certain that the liver extract must supply at least three additional factors, vitamin B<sub>6</sub>, factor W, and pantothenic acid. If the dogs are deprived of vitamin B<sub>6</sub> they will develop a severe microcytic anemia which responds readily to the administration of 60 micrograms of synthetic vitamin B<sub>6</sub> per day. When the basal is supple-

mented with vitamin B<sub>6</sub> alone there is no growth until pantothenic acid and factor W concentrates are added.

Thus it is important to follow the nicotinic acid therapy with foods rich in other members of the B complex. Nicotinic acid as such is an emergency measure. Our goal should be the modification of the diet so that the people existing on marginal diets would obtain nicotinic acid as well as other essentials from foods. This does not mean that certain foods low in nicotinic acid but relatively rich in other essentials could not be fortified when experimental work has shown the proper means of fortification. The dogmatic statement that foods must not be fortified with nicotinic acid or other synthetic vitamins should not be accepted until all the facts are available.

Let us now turn to the second question. Are other compounds equally as effective as nicotinic? Shortly after we demonstrated the effectiveness of nicotinic acid in the dog, Mr. Madden and I, in conjunction with Strong and Woolley,<sup>47</sup> tested the activity of a number of related pyridine derivatives. The active and inactive compounds are listed in Table II. It was immediately apparent that a rather specific structure is required for anti-black tongue potency. The alpha and gamma isomers of nicotinic acid (picolinic acid and isonicotinic acid) are completely inactive. All the compounds tested in which one of the ring hydrogens had been substituted (by a methyl or a carboxyl group) or in which a methyl group had been added to the ring nitrogen were inactive. The replacement of the carboxyl group of nicotinic acid by a sulfonic acid group or by a cyano group or the removal of the carboxyl entirely (i.e., pyridine) led in each case to inactive compounds.

It appears probable that in addition to the acid and its amide only those compounds possess anti-black tongue potency which are capable of oxidation on hydrolytic conversion to these substances in the body. Evidence for this view is based on the fact that alkyl substituted amide proved to be active as did the ethyl ester  $\beta$ -picoline which might be expected to be oxidized in the body to nicotinic acid showed a fair degree of activity. Nicotinuric acid was also active, which indicates that the body can hydrolyze this dipeptide. Subbarow, Dann, and Meilman<sup>48</sup> reported in a preliminary note that  $\beta$ -aminopyridine was highly active in the treatment of black tongue. When this compound was tried in our laboratory, we<sup>49</sup> found it to be completely inactive. In a later note Subbarow and Dann<sup>50</sup> confirmed our findings.

It is interesting that there is a close correlation between the results obtained in our work with dogs and those obtained by Dorfman, Koser, and Saunders<sup>51</sup> with the dysentery bacillus Since they found  $\beta$ -picoline to be completely devoid of growth-promoting activity the organisms evidently cannot oxidize the methyl group while the animal body can bring about this transformation to a limited extent

Recently there has been considerable interest in the activity of related pyrazine and thiazole compounds Dr Bills has prepared both the mono and the 2,3 dicarboxylic acid derivatives of pyrazine, and Spies (personal communication) has found that they show some activity in pellagra We have also found that they possess about one-tenth the activity of nicotinic acid in the treatment of black tongue Dr Schmelkes has sent us thiazole 5 carboxylic and it also shows some biological activity To date no compound has been found which is more effective than nicotinic acid or the amide

At this point we should say a word about the toxicity of nicotinic acid The work of both Chen, Rose and Robbins<sup>52</sup> and of Unna<sup>53</sup> indicates the very low toxicity of nicotinic acid and its derivatives Sodium nicotinate showed a toxicity in mice and rats only when fed at levels ranging from 4 to 7 grams per kilogram body weight The amide was found to be somewhat more toxic than the sodium salt Unna found that prolonged oral administration of 2 grams per kilogram daily of sodium nicotinate to rats, chickens, and dogs over periods up to 2 months failed to produce toxic symptoms The work of Chen, as well as that in our own laboratory showed that dogs receiving 2 gm of nicotinic acid per day for several days showed some toxicity However, Unna suggests that the toxicity may have been due to the acidity of the nicotinic acid since he observed no ill effects with the neutralized compound in even larger doses In any case there seems to be the same wide range between therapeutic dose and toxic dose for nicotinic acid as for the other vitamins

In addition to the above results practically all investigators have found that the administration of large amounts of nicotinic acid to human beings is often followed by sensations of heat and tingling of the skin This feeling is accompanied by flushing and rise in skin temperature In normal individuals the intravenous injection of 20 mg nicotinic acid or its salt will cause an increased skin temperature According to Spies, Bean, and Ashe<sup>52</sup> the chemicals effective in pellagra therapy do

not always produce flushing but those provoking the temperature rise are all effective therapeutic agents Sebrell and Butler<sup>54</sup> found reactions in some persons on continued treatment with daily doses as low as 30 mg by mouth They conclude that the occurrence of these transient reactions should not be allowed to interfere with the therapeutic use of large doses of nicotinic acid

As soon as the nutritional significance of nicotinic acid was recognized, it was generally assumed that its function in the animal body must be related to coenzymes I and II However, it was not easy to obtain direct evidence for this relationship Both coenzymes are very important in carbohydrate metabolism and they are supposed to differ in structure only by one molecule of phosphoric acid, yet they possess remarkable specificity in relation to the dehydrogenases with which they will react In most cases a substrate together with its dehydrogenase will react with one of the coenzymes but not with the other The quantitative estimation of the amount of coenzyme present in tissues is based upon this specificity Of the two factors, coenzyme I or cozymase is most easily estimated

The most obvious approach to any study on the function of nicotinic acid is therefore the estimation of the coenzyme content of the tissues from animals suffering from nicotinic acid deficiency Euler and co-workers<sup>55</sup> used this approach on rats but unfortunately a specific nicotinic acid deficiency was not produced in the rats Very recently Euler and co-workers<sup>56</sup> have presented results to show that tissues from rats on diets low in the B complex tend to be lower in nicotinamide and cozymase than those from normal rats However, it remains difficult to demonstrate an uncomplicated deficiency of the pyridine nucleotides or any of their precursors in the rat We have, therefore, used the dog and the pig in all of our studies

We have limited our work to coenzyme I and the amount in various tissues has been determined by the yeast fermentation method which has been employed by the Euler group The method is based on the principle that the addition of varying amounts of coenzyme to a washed yeast preparation will produce rates of fermentation which are proportional, within certain limits, to the amount of coenzyme I added The rate of CO<sub>2</sub> evolution is measured in a Barcroft differential manometer under very carefully controlled conditions The optimum levels of washed yeast, glucose, magnesium, manganese, hexose diphosphate, and

TABLE III

THE COENZYME I CONTENIS (EXPRESSED IN MICROGRAMS PER GM OF FRESH WEIGHT) OF VARIOUS ISSUES

<i>Animal</i>	<i>Liver</i>	<i>Kidney cortex</i>	<i>Brain gray matter</i>	<i>Gastrocnemius muscle</i>	<i>Blood</i>
Guinea pig	523 (4)*	503 (4)	107 (4)	662 (4)	65-89 (4)
Rat	1114 (6)	1077 (6)	353 (6)	782 (6)	84-106 (6)
Chicken	878 (3)	990 (3)	306 (3)	693 (3)	65-105 (15)
Dog	1185 (1)	1060 (1)	—	458 (1)	51-66 (4)
Human	—	—	—	—	20-35 (10)

\* Figures in parentheses indicate the number of animals used

buffer must be determined for each type of yeast used. Under these conditions the cozymase content of animal tissues may be determined by comparison with standard amounts of pure cozymase provided there is no loss of cozymase during the preparation of the animal tissues for analysis.

Dr Axelrod, working in our laboratory, has found that the following procedure allows practically complete recovery of the cozymase. The animal is sacrificed in the absence of anesthesia and the desired tissue removed immediately, cut into thin slices, and placed on slabs of solid carbon dioxide. The frozen tissue is ground to a fine powder, placed in boiling water, boiled for 2 minutes, and cooled immediately. A suitable aliquot can then be taken for analysis. When blood is analyzed the red cells are separated and placed directly in hot water.

In Table III are given the results obtained with several different tissues taken from guinea pigs, rats, chickens, dogs, and humans. It is apparent that cozymase content of the tissues from different species does not vary greatly in spite of the apparent difference in the nutritional requirements. The values given in this table are somewhat higher than those found in the literature due undoubtedly to the fact that great care was taken to prevent destruction of the cozymase during the process of extraction.

Our first studies on the effect of a nicotinic acid deficiency involved the determination of the cozymase content of the blood of normal dogs.

TABLE IV

## THE EFFECT OF A NICOTINIC ACID DEFICIENCY UPON THE COENZYME I CONTENT OF DOG TISSUES

Tissue	<i>Micrograms of coenzyme I per gram of fresh tissue</i>		
	Dog IV deficient	Dog V deficient	Dog VI normal
Kidney cortex	1180	1070	1000
Blood*	60	66	61
Liver	714	650	1185
Gastrocnemius muscle	295	427	490

\* No significant changes were found in the hematocrit values

and dogs suffering from black tongue. Throughout our entire work we have been unable to show any decrease in the blood even in very severe cases of black tongue. Similar results have been obtained with blood from pigs suffering from severe nicotinic acid deficiency. It is interesting that values for dogs range from 50 to 60 micrograms of cozymase per cc of whole blood and for pigs the value is less than 10 micrograms. In both cases all of the cozymase was found in the corpuscles.

Vilter, Vilter, and Spies<sup>45</sup> using the method of Lwoff found a decrease in the cozymase content of the blood of pellagrins and an increase upon the administration of nicotinic acid. Kohn,<sup>46</sup> however, found no difference between the blood of normal and pellagrous patients but did find an increase even in normal patients upon administration of nicotinic acid. Our studies on humans carried out in cooperation with Dr. Edgar Gordon agree with those of Kohn. The value in normal patients was found to be 20-30 micrograms per cc of blood, which may increase to 50-60 micrograms upon the ingestion of 100 mg nicotinic acid per day. When the high level is established and the nicotinic acid is no longer supplied, the cozymase gradually decreases to the normal level during a period of about two weeks.

Our next approach was the estimation of cozymase in the tissues taken from the various animals. At first we did not have pure cozymase as a standard, but even in these studies it was evident that both the liver

TABLE V

## COZYMASE AND NICOTINIC ACID CONTENT OF BIOLOGICAL MATERIALS

	<i>Cozymase</i> mg per 100 gm fresh wt	<i>Nicotinic acid</i> calculated from cozymase, mg per 100 gm fresh wt	<i>Nicotinic acid</i> found, mg per 100 gm fresh wt
Liver, beef	70	12.9	26.1
Liver, pork	52	9.6	33.0
Muscle, beef	31	5.7	13.8
Muscle, rat	20*	3.7	—
Blood, human	2.3	36-54	38**
Yeast, brewers	50*	9.2	24.0
Yeast, bakers	25*	4.6	12.0

\* Euler — \*\* Swaminathan

and muscle tissue from deficient dogs contained considerably less than the same tissues from normal dogs. No differences could be detected in the kidney and brain. After the pure cozymase was made available to us by Dr. von Euler, it was possible to calculate the actual amount in the tissues.

The results obtained with one normal dog and two black tongue dogs are given in Table IV. From these figures it is evident that there may be a significant decrease in the liver and muscle depending upon the severity of the symptoms. Similar results have been obtained with pigs. The muscle of the deficient pigs showed a much greater decrease than in the case of the dogs.

It is significant that the brain, kidney, cortex, and blood maintained their normal coenzyme I content under the conditions of our experiments. Perhaps a normal level in these tissues is absolutely essential and a decrease is incompatible with life. In the case of liver and muscle, the vital functions can apparently be maintained although presumably to a greatly reduced degree in the absence of their normal content of coenzyme I. Under more severe conditions changes may also take place in tissues other than the liver and muscle. Whether the decrease in the liver and muscle is sufficient to account for the gross symptoms observed

cannot be answered at this time. However, it is quite probable that the rapid improvement noted both in humans and animals when nicotinic acid is administered is due to the rapid formation of cozymase when the nicotinic acid part of the molecule is made available.

Further evidence for the direct relationship of nicotinic acid found in animal tissues is present as cozymase. We have determined the cozymase content of a number of edible tissues which were also assayed for nicotinic acid potency on dogs. Some of these values are shown in Table V.

If the cozymase is converted to an equivalent amount of nicotinic acid we find that this amount makes up an appreciable amount of the total nicotinic acid. Part of the nicotinic acid must be present as coenzyme II and there is undoubtedly some free nicotinic acid and amide. More definite comparisons can be made when accurate chemical methods for these tissues are available.

In summary we may say that nicotinic acid has a history very similar to that of thiamin and riboflavin. The availability of pure nicotinic acid has not only given us a practical means of combating pellagra but has aided us in understanding some of the metabolic processes which are disturbed during pellagra. Such an understanding will aid in the diagnosis of a nicotinic acid deficiency before the gross symptoms of pellagra develop. We may look for similar results with vitamin B<sub>6</sub> and pantothenic acid as well as other unrecognized factors.

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Dresden, Steinkopff, 1940, 209 p

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N Y, Commonwealth Fund, 1939, 306 p

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N Y, Macmillan, 1939, 205 p

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Chicago, Physicians' Record Co, 1939, 361 p

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Dresden, Steinkopff, 1939, 285 p

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N Y, Oral Hygiene Committee, [1939], 202 p

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London, Milford, 1939, 370 p

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N Y, Reinhold, 1939, 384 p

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N Y, Dutton, 1940, 243 p

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N Y, Appleton-Century, [1940], 227 p

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Boston, Little, 1939, 654 p

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Roma, "Universitas" Società Editrice, 1939, v 1 & 2

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London, Cassell, [1939], 563 p

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Dresden, Steinkopff, 1940, 169 p

## PROCEEDINGS OF ACADEMY MEETINGS

## STAGED MEETINGS

JANUARY 4—*The New York Academy of Medicine Annual Meeting* Executive session—a] Reading of the Minutes, b] Presentation of diplomas ¶ Presentation of annual reports (to be read by title) the Council, the Trustees, the Treasurer, Committees ¶ Papers of the evening Chemotherapy including sulfapyridine and allied compounds—c] General considerations, Francis G Blaue Sterling Professor of Medicine, Yale University School of Medicine, b] Pneumonia, Norman Plummer, Instructor in Medicine, Cornell University School of Medicine, c] Toxic effects, William S Tillett, Professor of Medicine, New York University College of Medicine ¶ Report on election of members

JANUARY 18—*The Harvey Society in affiliation with The New York Academy of Medicine* The fourth Harvey lecture, "Heredity and the Development of Early Abnormalities in Vertebrates," L C Dunn, Professor of Zoology, Columbia University

## SECTION MEETINGS

JANUARY 2—*Dermatology and Syphilology* Presentation of cases—a] New York University, College of Medicine and Bellevue Hospital, b] Miscellaneous cases ¶ General discussion ¶ Executive session

JANUARY 5—*Surgery* Reading of the minutes ¶ Presentation of cases—a] Recurrent acute pancreatitis, James Edwin Thompson b] Recurrent acute pancreatitis, Frederick Henry Amendola Discussion, Henry Wisdom Cive, e] Primary adenocarcinoma of the jejunum with resection, Nelson Warren Cornell, Discussion, N Chandler Foot, d] Cast of the pancreas, complete excision, Result after 6 months, John H Gillock

Discussion, Frank J McGowin ¶ Papers of the evening—1] Clinical value of serum amylase studies in pancreatic disease, Edward F Lewison (by invitation), Discussion, Percy Klingenstein, b] Carcinoma of the head of the pancreas, William Buckley Parsons, Discussion William Crawford White, c] Studies in pancreaticogastrostomy and partial pancreatectomy in animals, Frank Glenn, Discussion William Frank McFee ¶ General discussion ¶ Executive session

JANUARY 9—*Combined Meeting, Section of Neurology and Psychiatry and the New York Neurological Society* Papers of the evening—a] Cerebral arteriography by means of a rapidly excreted organic iodide compound, Sidney W Gross, Discussion, Cornelius G Dyke, Irvine H Marshall (by invitation), Lawrence Poole (by invitation), b] Recent experimental disclosures concerning the functions of the frontal lobes, John F Fulton (by invitation), Discussion, Richard M Brickner, Lucretta Bender, Kurt Goldstein (by invitation), John E Searff, c] Pupillography, its significance in clinical neurology, Otto Loewenstein (by invitation), Discussion, John F Fulton (by invitation), M Davidson, Bernard Sachs ¶ Executive session

JANUARY 10—*Historical and Cultural Medicine* Reading of the minutes ¶ Paper of the evening—The Renaissance of Anatomy, from Mondino to Leonardo, Professor A Castiglioni, Padua, Italy (by invitation) ¶ Discussion, Victor Robinson (by invitation), Leon Baumgutner (by invitation), George Rosen (by invitation) ¶ General discussion

JANUARY 11—*Pediatrics* Program presented by members of the Department of Pediatrics of Harvard University Medical School Reading of the minutes ¶ Papers of the evening—a] Blood ascorbic acid concentrations in terms of plasma red

cells and white cells, Allan M Butler (by invitation), b] Extraacellular fluid volume, James L Gamble (by invitation), c] Variability of the clinical and hematological manifestations of leukemia in childhood, Louis K Diamond (by invitation), d] The criteria for ligation of the patent ductus arteriosus in the light of the first one and a half-years' experience, John P Hubbard (by invitation), Robert E Gross (by invitation) ¶ General discussion ¶ Executive session

JANUARY 15—*Ophthalmology* Instruction hour 7:00 to 8:00—Non-suppurative diseases of the cornea, Ralph I Lloyd ¶ Demonstration of Slit Lamp Cases 8:00 to 8:30, Gordon M Bruce, Girolamo Bonaccolto, Milton Berliner ¶ Reading of the minutes ¶ Presentation of cases—a] Motion picture demonstration of unusual neuro-ophthalmological conditions, S Philip Goodhart, Benjamin Balser (by invitation), b] Repair of entropion, Raymond Meek ¶ Papers of the evening—¶ Diagnostic significance of central scotoma, Frank B Walsh, Baltimore (by invitation), Discussion, John Evans, b] Sclerocorneal sutures, John M McLean, Baltimore (by invitation) ¶ Executive session

JANUARY 16—*Medicine* Reading of the minutes ¶ Papers of the evening—a] Trauma and its relationship to heart disease, Louis Faugeres Bishop, Discussion, Arthur M Master, b] Weil's disease in New York City, Elliston Farrell (by invitation), Discussion ¶ General discussion

JANUARY 17—*Genito-Urinary Surgery* Reading of the minutes ¶ Papers of the evening Symposium on Experimental and clinical phases of sex hormone therapy—a] Current errors about sex and sex hormones, James F McCahey, Department of Urology, Jefferson Medical School (by invitation), b] Indications for hormone therapy in glandular deficiencies, Walter M Kearns, Department of Urology, Marquette University (by

invitation), c] Evaluation of hormone therapy in diseases of the genito-urinary system, Norris J Heekel, Department of Urology, Rush Medical School (by invitation) ¶ General discussion, Earl F Engle, Columbia University ¶ Executive session

JANUARY 17—*Otolaryngology* Reading of the minutes ¶ Papers of the evening—a] Dental reactions of the temporomandibular joint of interest to otolaryngologists (motion pictures, lantern slides), Sidney E Riesner, DDS (by invitation), Discussion, Edmund Prince Fowler, Sr, Solomon Finegan, b] Voice anomalies of hysterical origin Psychosomatic interrelationship (slides, recordings), James Sonnett Greene, Discussion, Oskar Diethelm, Cornell University Medical College (by invitation), Irving W Voorhees (by invitation) ¶ Executive session

JANUARY 23—*Obstetrics and Gynecology* Reading of the minutes ¶ Papers of the evening—a] Potency evaluations of the commercial female hormone preparations, Bernard L Cimberg (by invitation), Stanley F Goldman (by invitation), Discussion, Edwin G Langrock, b] Studies in artificial ovulation with the hormone of pregnant mares' serum (motion pictures in color), Samuel I Siegler (by invitation), Discussion, Raphael Kurzrok

*Orthopedic Surgery*—There was no meeting of the Section of Orthopedic Surgery in January because of the annual meeting of the American Academy of Orthopedic Surgeons which was held January 21-25, at the Hotel Statler, Boston

#### AFFILIATED SOCIETIES

JANUARY 15—*New York Roentgen Society in affiliation with The New York Academy of Medicine* Case reports—¶ Skeletal changes induced by the administration of estrogen, Charles J Sutro (by invitation), b] An unclassified destructive bone lesion simulating a malignant

nant tumor, Louis Lichtenstein (by invitation), c] A review of 58 cases of tabetic arthropathy, Maurice M Pomeranz, Abraham S Rothberg (by invitation) ¶ Paper of the evening—Findings in cases generally misinterpreted as cortical bone abscess or sclerosing osteomyelitis of long bones, Henry L Jaffe  
¶ Discussion ¶ Executive session

JANUARY 25—*New York Pathological Society in affiliation with The New York Academy of Medicine* Case reports—  
a] A case of thromboarteritis of the pulmonary artery with chronic obstruc-

tion in the pulmonary circulation, B M Vance, Chief Medical Examiner's Office, b] Contralateral adrenal atrophy associated with cortical adrenal neoplasm, Tobias Weinberg, Mt Sinai Hospital ¶ Papers of the evening—a] The influence of sulfanilamide and sulfapyridine upon the evolution of experimentally induced pneumococcus pneumonia in rats, David Goldstein (by invitation), Irving Graef, New York University College of Medicine, b] Aplastic anemia, Cornelius P Rhoads (by invitation), Memorial Hospital ¶ Executive session, election of officers

#### DEATHS OF FELLOWS

BREWER, GEORGE EMERSON 150 East 73 Street, New York City, born in Westfield, New York, July 28, 1861, died in New York City, December 24, 1939, received the degrees from Hamilton College of A B, 1881, M A, 1884, LL D, 1916, M D from Harvard University in 1885, and hon D Sc from Columbia University in 1929, elected a Fellow of the Academy October 3, 1889

Dr Brewer was emeritus professor of surgery at the College of Physicians and Surgeons from 1917 until the date of his death, having served that institution as assistant demonstrator in anatomy, 1892-1900, instructor in surgery 1900-1903, professor of clinical surgery, 1903-1914, and professor of surgery, 1914-1917. He was consulting surgeon to the Roosevelt, City, Woman's and Presbyterian Hospitals of New York City, Christ Hospital at Jersey City, Perth Amboy Hospital at Perth Amboy and Muhlenberg Hospital at Plainfield, New Jersey

Dr Brewer was a Fellow of the American College of Surgeons, and the Royal College of Surgeons (Ireland), a member of the American Surgical Association and its president in 1919, the New York Surgical Society, the American Society of Genito-Urinary Surgeons, the Society of Clinical Surgeons and its president, 1901-04, Société Internationale de Chirurgie, Société Internationale d'Urologie, the American Medical Association and the New York County and State Medical Societies

In 1917, Dr Brewer went to France to direct Base Hospital No 2 which relieved General Hospital No 1 of the British Expeditionary Force at Etretat. He was promoted to the rank of chief surgeon of the 42nd Division and consultant in surgery to the First Corps, First Army of the American Expeditionary Force and later promoted to the rank of colonel

Dr Brewer was the author of a "Text Book on Surgery," and "Surgical Diagnosis," and many articles on anatomical and surgical conditions

LEWIS, ROBERT 10 East 64 Street, New York City, born in New York City, March 8, 1862, died in New York City, December 20, 1939, graduated in medicine from the College of Physicians and Surgeons in 1885,

elected a Fellow of the Academy May 6, 1897, served as Chairman of the Section of Otology in 1910, and designated a Fellow in Otolaryngology in 1933.

Dr Lewis was clinical professor emeritus of otolaryngology at the College of Physicians and Surgeons, Columbia University, from July 1939 until his death, having served that institution as instructor in otology, 1896-1908, professor of clinical otology, 1908-1916, professor of clinical laryngology and otology, 1916-1929, professor of clinical otolaryngology, 1929-1938, and clinical professor of otolaryngology, 1938-1939. From 1901 until 1928, he was surgeon to the aural department of the New York Eye and Ear Infirmary, and in 1928 he was elected consulting surgeon. He was also consulting otolaryngologist to the New York Society for Relief of the Ruptured and Crippled, Flushing, St Francis and Set View Hospitals.

Dr Lewis was a diplomate of the American Board of Otolaryngology, a Fellow of the American College of Surgeons and a member of its Board of Governors, 1921-1925, a member of the New York Otological Society and its president, 1911-1913, a member of the American Otological Society and its president in 1920, a member of the

American Rhinological, Laryngological and Otological Society and its vice-president in 1919, a member of the American Medical Association and the New York County and State Medical Societies, and an alumnus of the Federation of Columbia University and its vice-president in 1919.

Dr Lewis contributed treatises on otological topics to "Reference Handbook of Medical Sciences," to "The American Practice of Surgery" and to medical journals.

MENDELSON, WALTER 639 Church Lane, Germantown, Philadelphia, Pennsylvania, born in Germantown, April 9, 1857, died in Germantown, January 18, 1940, graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1879, elected a Fellow of the Academy June 5, 1884.

Dr Mendelson was a member of the Board of Trustees of Columbia University, 1913-1918, and served as Chairman of the Board of Trustees of the College of Physicians and Surgeons in 1923. He was president of the Alumni Association of the College of Physicians and Surgeons, 1910-1919, and was awarded the Alumni Medal of Columbia University, in 1933.

BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



APRIL 1940

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CHEMOTHERAPY WITH THE SULFONAMIDE  
DERIVATIVES GENERAL PRINCIPLES\*

FRANCIS G. BLAKE

Sterling Professor of Medicine, Yale University School of Medicine

**F**Ollowing the introduction of the sulfonamide group of drugs as bacterial chemotherapeutic agents and their first reported clinical application by Foerster<sup>1</sup> in 1933, the use of these compounds in the treatment of infections in man very soon became so apparently successful that they were already widely used clinically before much was known concerning the scope and nature of their chemotherapeutic properties in experimental infections in animals, their mechanism of action, their toxicity, and the principles governing their absorption, distribution, conjugation and excretion. Numerous compounds appeared in rapid succession under a variety of confusing names with conflicting claims concerning their relative merits in this or that type of infection. Gradually, however, careful laboratory investigations began to parallel and influence clinical application, until latterly they have begun quite properly to precede the introduction of new compounds, prepared with the purpose of extending the usefulness of the sulfonamide derivatives in human disease.

\* Presented January 4, 1940 at the Annual Meeting of The New York Academy of Medicine  
From the Department of Internal Medicine, Yale University School of Medicine

Since the intelligent use of these drugs must be based upon an adequate understanding of their scope and mode of action and their pharmaceutical properties, it is my purpose in this general discussion to review the development of knowledge concerning these problems I shall endeavor to point out their bearing on clinical therapeutics Of necessity I must limit myself to the high-lights since the time available will not permit me to fill in much in the way of detail

The sulfonamide group of drugs center around para-amino-benzene sulfonamide, first synthesized by Gelmo<sup>2</sup> in 1908 Though not the first compound introduced into chemotherapy, it has become the hub of the wheel and now bears the medical designation, sulfanilamide For the purposes of the present discussion its derivatives may be conveniently placed in two groups

The first group, which includes the original prontosil used by Domagk,<sup>3</sup> consists of those derivatives in which substitutions have been made in the para-amino group Of these the more important are the azo dyes prontosil (Mietzsch and Klarer,<sup>4</sup> 1932, Domagk,<sup>3</sup> 1935) and the more soluble neoprontosil (Domagk,<sup>5</sup> 1935), and benzyl sulfanilamide (septazine, Goiszedet et al,<sup>6</sup> 1936)

The second group consists of those derivatives in which substitutions have been made in the sulfonamide group at the other end of the benzene ring leaving the para-amino group free Among these may be mentioned sulfanilyl sulfanilamide (Rosenthal et al,<sup>7</sup> 1937) and its dimethyl derivative (Domagk,<sup>8</sup> 1937), diamino-diphenyl sulphone (Buttle et al,<sup>9</sup> 1937), sulfapyridine (Whitby,<sup>10</sup> 1938), and sulfathiazole (Fosbinder and Walter,<sup>11</sup> 1939) and its methyl derivative sulfamethylthiazole (Herrell and Brown,<sup>12</sup> 1939) recently introduced and now being submitted to experimental investigation in the laboratory and the clinic

The reason for grouping the sulfonamide derivatives in this fashion, which will, perhaps, become more evident as I proceed, is because it would appear to bear at least some relation to breadth and effectiveness as well as mode of therapeutic action

Comparative studies in experimental animals on the protective action of the sulfonamide group of drugs, and *in vitro* observations on their bacteriostatic and bactericidal properties, beginning with the original observations of Domagk<sup>3</sup> on the curative action of prontosil on  $\beta$ -hemolytic streptococcal infection in mice down to the most recent observations on sulfamethylthiazole<sup>12</sup> on staphylococcal infections have covered

a wide range of bacteria and viruses. At first glance the results reported by various investigators often appear conflicting, no doubt in large part due to numerous variables which inevitably occur in experiments of this kind before an acceptable, standard technique has been evolved.

In spite of these difficulties certain high-lights stand out, which may serve to bring some degree of order out of the apparent confusion, even though many points still remain at issue.

The first significant experimental observations were, of course, those of Domagk,<sup>15</sup> that the azo dyes, prontosil and neoprontosil, though exerting no demonstrable bactericidal or bacteriostatic action *in vitro*, were nevertheless highly effective *in vivo* against virulent hemolytic streptococci, 100 per cent of treated mice surviving 10 ml d for seven days in his first recorded experiment. These observations have been amply confirmed<sup>16</sup> by numerous subsequent observers, though in general without quite such perfect results.

The second highly important contributions were those of the Tréfouels<sup>11</sup> and their collaborators, who showed that sulfanilamide by itself without the azo linkage was not only effective against hemolytic streptococcal infections in mice but also possessed active bacteriostatic properties *in vitro*. These observations provided the basis for the now widely accepted view that the azo dyes, prontosil and neoprontosil, are changed in the animal body and owe at least the major portion of their activity to the liberation of sulfanilamide, which is the active component, a view well supported by the studies of Colebrook, Buttle and O'Meara,<sup>15</sup> Fuller,<sup>16</sup> and Long and his collaborators.<sup>17</sup>

If this be correct, sulfanilamide weight for weight should be more effective as a chemotherapeutic agent than prontosil, neoprontosil and benzyl-sulfanilamide, provided variations in absorption are not so great as to render comparisons invalid. Though the pitfalls in such comparisons are numerous and there is not complete agreement, I believe it safe to state that the majority of workers have recorded experiments indicating that sulfanilamide, weight for weight, is at least equivalent to or superior to the prontosils and benzyl compounds, so far as chemotherapeutic effectiveness against hemolytic streptococci is concerned. Not only does this appear to be so with hemolytic streptococci but also in the case of many other bacteria. Among them may be included meningococci, pneumococci, staphylococci, Friedlander's bacillus and brucella.

If we turn now to the other group of compounds in which substitu-

tions in the sulfonamide group have been made, the picture appears quite different. Here we find compounds which are at least equivalent to, if not superior to, sulfanilamide in experimental streptococcal and meningococcal infections. At the same time the scope of their effectiveness appears to be wider. Conspicuous among these is sulfapyridine, the superiority of which in pneumococcal infections is already well established. Animal experiments, furthermore, suggest that it is more effective than sulfanilamide in staphylococcal<sup>18</sup> and Friedlander's bacillus<sup>13</sup> infections. Two newcomers, still in the stage of experimental investigation, are sulfathiazole and sulfamethylthiazole. In preliminary studies by McKee, Rake, Greep and van Dyke,<sup>19</sup> sulfathiazole would appear at least equivalent to sulfapyridine, so far as hemolytic streptococci, pneumococci, and meningococci are concerned, while sulfamethylthiazole may perhaps be even more effective in staphylococcal infections,<sup>12</sup> though further data are necessary to confirm this.

Although comparative experiments would appear to suggest that the differences in scope and effectiveness exhibited by these two groups of sulfonamide derivatives are largely quantitative, this cannot be accepted as proved at present because standard methods for comparative assay have not been used. As emphasized by Marshall,<sup>20</sup> strains of organisms, size of inoculum, amount, spacing and method of dosage, duration of therapy and period of observation have varied so much from worker to worker that accurate quantitative comparison is impossible with active compounds having different ratios of absorption and excretion.

Whether the differences exhibited indicate actual qualitative differences in specificity for different organisms is likewise impossible to answer with certainty at present. The much greater effectiveness of sulfapyridine against the pneumococcus, for example, would suggest specificity, but since there is some evidence that it is also more effective against hemolytic streptococci,<sup>10,13,18</sup> staphylococci<sup>13,18</sup> and Friedlander's bacilli,<sup>13</sup> this may be merely a quantitative difference.

The relative importance of the amino group and the sulfonamide group in determining chemotherapeutic activity likewise cannot be stated dogmatically at present. Active compounds, with rare and somewhat dubious exceptions, either have a free amino group in the para-position to the sulfonamide group or a substituted group (nitro group or azo linkage) which is readily changed to an amino group in the animal body. Substitutions which do not permit change to an amino group,

e.g., acetyl sulfanilamide, in general, appear to be inactive.

Since, by definition the group of compounds under discussion contain sulfur in the sulfonamide group it is irrelevant to enter into a discussion here as to whether sulfur is an essential component for chemotherapeutic activity, though it may be remarked in passing that this is unlikely (Rosenthal, Bauer and Elvove<sup>21</sup>).

Whatever the ultimate solution of the foregoing problems may be, the clinical significance of these comparative *in vivo* and *in vitro* studies of the sulfonamide derivatives against various bacteria is obvious, since they point the way to the selection of the most effective drugs among the various compounds available. Furthermore, they suggest at least that the road to further improvement in scope and effectiveness of action lies along the way of substitutions in the sulfonamide group.

It hardly need be pointed out, however, that other factors besides relative chemotherapeutic efficiency in mice and bacteriostatic activity in the test tube may of necessity modify the selection of the most suitable drug for practical therapeutics in man, such factors as primary toxicity, absorbability, and human idiosyncrasy to untoward reactions, to mention a few.

For example, the experimental studies indicate clearly the superiority of sulfapyridine over sulfanilamide in pneumococcal infections, an observation which has found ample confirmation in the clinic. In hemolytic streptococcal infections on the other hand, the fact that sulfapyridine seems to possess some superiority in laboratory studies, would hardly justify at present the complete abandonment of sulfanilamide in favor of sulfapyridine, in view of the poorer absorbability, greater variability in acetylation and greater tendency to induce untoward reactions, such as nausea, vomiting and hematuria, exhibited by sulfapyridine. In the end, of course, carefully controlled studies in patients, so well illustrated by the studies of the last year on sulfapyridine in lobar pneumonia, must determine the issue in favor of this or that compound in any given infection.

It is now so well established by the work of numerous investigators that the therapeutic activity of the sulfonamide compounds is dependent upon their bacteriostatic action, rather than upon a capacity to stimulate the defensive mechanisms of the host, that it seems hardly necessary in this discussion to marshal the evidence in support of this view. Nor does it seem profitable to enter into a discussion of the several theories

concerning the mechanism by which bacteriostasis is brought about, since none of them has as yet attained the position of final proof

A few points with clinical implications, however, emerge from the welter of *m vitro* and *m vivo* studies on mechanism of action which may be briefly touched upon

The failure of the azo dyes to exhibit bacteriostatic action *m vitro* as contrasted with sulfanilamide and those derivatives in which substitution has been made in the sulfonamide group has already been mentioned and its implications pointed out

*In vitro* experiments, principally on hemolytic streptococci but also on other bacteria, with concentrations of sulfanilamide equivalent to those attained in the blood of patients and with a suitably small initial inoculum, have commonly resulted after an initial lag period in variable degrees of bacteriostasis without true bactericidal effect. In the presence of whole blood, as contrasted with blood deprived of leukocytes, prompt killing of streptococci occurs. Similarly a much greater bacteriostatic action and frequently a bactericidal action in the presence of whole blood has been found in our laboratory by Dr Haury with sulfapyridine and staphylococci. These observations have strongly suggested that cooperative activity on the part of phagocytic and perhaps other immunity mechanisms of the host is important or essential in the final recovery of patients being treated with the sulfonamide drugs. Numerous animal experiments, among others those of Gay and Clark<sup>22</sup> in streptococcal infection in rabbits and Menefee and Poston<sup>23</sup> on brucella infections in guinea pigs, strongly support this view. When taken in conjunction with the oft repeated observation, particularly in streptococcal and staphylococcal infections, that relapse of infection with ultimate death often occurs in a considerable proportion of experimental animals following cessation of treatment, this fact assumes a position of significant importance in human therapeutics, particularly in those infections which do not naturally run a relatively brief, self-limited course to recovery.

To cite specific examples, facial erysipelas in adults in general runs a relatively short, self-limited course. It responds dramatically to sulfanilamide therapy and relapses are exceedingly rare even though therapy be discontinued relatively soon after the temperature has fallen to normal. By and large the same may be said to be true in lobar pneumonia treated with sulfapyridine, provided treatment is carried till the 7th to 9th day from onset, at which time the immunity mechanism commonly

comes into operation Erysipelas of the new-born, on the other hand, usually runs a progressive course with generalization of the infection and ultimate death Likewise responding brilliantly to early treatment, relapse is apt to occur with early cessation of treatment

Streptococcal sinusitis, mastoiditis and sepsis, gonococcal prostatitis and staphylococcal pyemia provide other examples in which initial response to chemotherapy may give a false sense of security, masking the fact that infection is still smoldering in local suppurative foci, ready to flare up when chemotherapy is discontinued, a problem ably discussed recently by Converse<sup>24</sup> in the case of otitic infections

Obviously, the problem of combined chemo and serum therapy versus chemotherapy alone in pneumococcal, meningococcal, and gas bacillus infections as well as others, is brought sharply into focus by the laboratory studies which indicate the cooperative role of immunity mechanisms in fortifying the chemotherapeutic action of the sulfonamide derivatives, but lack of time and the sparsity of adequately controlled comparative studies in man induce me to pass it by without further discussion Nor shall I comment on the important observations of White and Parker<sup>25</sup> on the influence of temperature and those of Lockwood<sup>26</sup> on the influence of nutritional environment on the bacteriostatic action of sulfanilamide, since their possible clinical significance is not yet clearly apparent, though the latter, as suggested by Lockwood, may have an important bearing on the tendency for bacteria to survive in walled off suppurative lesions unless these be surgically drained

Pharmacological studies, conspicuously those of Marshall<sup>20</sup> and his collaborators, have likewise contributed much of value to the practical application of chemotherapy in man These studies have been concerned particularly with problems of toxicity, absorption, distribution in the body, conjugation to the inactive acetyl derivatives, and excretion They have had an especially useful bearing on problems of amount and spacing of dosage in relation to establishment and maintenance of adequate blood levels The development of Marshall's method<sup>27</sup> for the quantitation of blood concentrations of total and free sulfonamide compounds has provided not only a useful guide to dosage but has made it possible to acquire information concerning the relation of blood levels to therapeutic effect and untoward reactions in patients under treatment

Comparative observations on blood concentrations following a single dose *per os* of 0.1 gm./K in dogs indicate a considerably more rapid

absorption of sulfanilamide than of sulfapyridine or sulfathiazole. At the same time the percentage of administered drug recovered in the urine during the ensuing twenty-four hours indicates a much more complete absorption and a somewhat more rapid rate of diffusion and excretion for the former. These observations find their counterpart in clinical observations showing the range of blood concentrations of sulfanilamide<sup>27</sup> and sulfapyridine<sup>28</sup> and a few recent observations on sulfathiazole<sup>29</sup> four hours after an initial dose *per os*. They indicate the greater urgency for an initial intravenous treatment with sulfapyridine than is the case with sulfanilamide in critically ill patients in whom it is desirable to establish an adequate concentration in the blood and body fluids as rapidly as possible.

Furthermore, the more rapid rate of excretion in the case of sulfanilamide suggests that treatment every four hours, day and night, is perhaps more essential for the maintenance of continuously adequate blood levels with this drug than may be the case with sulfapyridine. At least it has been our experience that treatment at six hour intervals with sulfapyridine will, in many instances, maintain an adequate blood level, once established, and even at eight to twelve hour intervals under parenteral treatment<sup>30</sup> by hypodermoclysis or intravenously. The problem is complicated in man, by so much individual variation from patient to patient that wider spacing of dosage with sulfapyridine than the customary four hour interval cannot at present be advocated as a routine but should be resorted to only when the presence of the higher range of blood levels indicates that it is permissible in a particular individual.

Pharmacological observations on the conjugation of sulfanilamide in animals have shown so much species difference in the capacity to convert sulfanilamide to the inactive acetyl compound that it has been found necessary to study this problem in man. Marshall<sup>27</sup> found that 10 to 20 per cent of the total sulfanilamide in the circulating blood was in the conjugated form and Stewart, Rourke and Allen<sup>31</sup> have shown that the ratio between free and acetyl sulfanilamide varies considerably from individual to individual. In the case of sulfanilamide, however, the degree of acetylation in man and individual variation would not appear to be of sufficient magnitude to be of clinical import and in practical therapeutics may be disregarded. A few preliminary observations<sup>29</sup> in patients treated with sulfathiazole and sulfamethylthiazole suggest that the same may hold for these compounds, but more extensive studies are

necessary before the possible range of individual variation will be known.

With sulfapyridine, on the other hand, the picture is quite different. The degree of acetylation may vary unpredictably over a wide range from patient to patient.<sup>30,32</sup> Recognition of this fact is of great importance in therapeutics if blood levels are to be used as a guide to amount and spacing of dosage, for a low or falling concentration of free sulfapyridine may be mistakenly regarded as an indication for increasing dosage when, in fact, the total concentration is rising with an increasing proportion of acetyl sulfapyridine present. On more than one occasion I have seen this mistake made, to be followed by gross hematuria, colic, temporary anuria and azotemia.

I have used the phrase adequate blood concentration without specifying what that may be, and I must confess to some degree of uncertainty concerning this, an uncertainty which has arisen from the now well established and perhaps unexpected finding that many cases of pneumococcal lobar pneumonia respond as promptly and dramatically to sulfapyridine with blood levels of free sulfapyridine under 5 mg per cent as do those with higher levels.<sup>30</sup> Quite early in the use of sulfanilamide in hemolytic streptococcal infections, 10 mg per cent or thereabouts was somewhat arbitrarily advanced as a desirable and necessary blood concentration for satisfactory therapeutic results and there can be no doubt that experience has shown that blood concentrations at this level are effective. Since adequate comparative data on the possible effectiveness of lower blood concentrations are not available, it is of no value to discuss the point, further than to suggest that it might be desirable to reexamine this question in the light of the results with sulfapyridine in pneumococcal pneumonia.

I have purposely not touched upon the general problems of toxicity and untoward reactions since they are to be discussed by a subsequent speaker on this program. If I have disappointed you by using the subjunctive more than you would like, I can only say that it has seemed to me the part of wisdom to be neither too positive nor too dogmatic in our present state of fragmentary, though rapidly increasing knowledge concerning the general principles involved in chemotherapy with the sulfonamide derivatives. That the future of chemotherapy will witness advances equal to or more brilliant than those of the last few years, there seems little doubt.

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## CHEMOTHERAPY OF PNEUMONIA\*

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ANY reports have appeared in the literature describing the use of sulfapyridine in the treatment of pneumonia. It is significant that all of these reports from the first one by Evans and Gaisford have presented favorable evidence. Already it is possible to assemble a series of cases, fully enough studied and of sufficient size so that from it some rather definite conclusions on the efficacy of the drug may be obtained. The gross mortality rate of lobar pneumonia varies greatly from year to year, even in the same locality or in the same institution. However, when similar age groups are included, it is safe to compare the results of treatment in different series of the same type, and it is even more reliable when the comparison is between bacteremic or non-bacteremic cases of a particular type.

The striking reduction in mortality rates in the more common types of pneumonia offers the most convincing evidence of the value of sulfapyridine. In order to make an analysis by types, it is possible to collect from the literature 966 cases of pneumococcus pneumonia in adults, in this geographical area, treated with sulfapyridine. A small percentage of these patients received anti-pneumococcus serum also, but it is impossible to separate these from the rest of the group. For comparison we are fortunate in having available the very large series of cases collected by Heffron in which he has attempted to establish the fatality rates for lobar pneumonia and for the different types in the United States and Canada.

Type I pneumonia, in Heffron's series of 2,314 cases without specific therapy, had a mortality rate of 29.0 per cent. During the past year, in the United States and Canada 193 cases of type I infection treated with sulfapyridine have been reported. Twelve deaths occurred, giving a fatality rate of 6.2 per cent. Heffron's series includes 351 cases of

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type I pneumonia with bacteriemia, and in this group the mortality rate was 58.1 per cent Contrast this figure with one of 13.9 per cent in forty-three bacteremic type I cases treated with sulfapyridine

The results obtained in type II and type III pneumonias are even more impressive because these diseases never showed the marked response to specific serum that has been demonstrated in type I and in some of the higher types There have been sixty-three patients with type II infection treated with sulfapyridine with four deaths, a mortality of 6.3 per cent Only seven of these patients showed positive blood cultures, and of these two died Heffron shows mortality rates of 36.6 per cent in untreated type II pneumonia, and 74 per cent for bacteremic type II A recent communication from Anderson and his associates in Glasgow on seventy cases of type II pneumonia treated with sulfapyridine shows a death rate of 8.0 per cent Twenty-five of the seventy cases, or 36 per cent, also had bacteriemia, and of these 16 per cent died Type III, the most dreaded of the types, in Heffron's cases shows a fatality rate of 46.0 per cent in the gross series, and 86.1 per cent in the bacteremic group In the sulfapyridine series, there are 156 type III pneumonias with a mortality of 15.4 per cent, and in this group eighteen had bacteriemia, and 38.9 per cent died

The total series of 966 pneumococcus pneumonias in adults treated with sulfapyridine shows a mortality rate of 8.5 per cent as compared with 32.8 per cent in some nineteen thousand similar cases without specific treatment analyzed by Heffron One hundred and twenty bacteremic cases including all types gave a mortality percentage of 26.7 to be contrasted with 61.8, Heffron's calculated figure

The clinical response to sulfapyridine is almost as remarkable as the reduction in mortality rate With almost constant regularity the temperature drops to normal within 24 to 36 hours after therapy is instituted The pulse becomes slower and less bounding, the respiration slower and more normal At this stage, the patient no longer seems critically ill, but does remain toxic and uncomfortable The color is poor, he is restless and quite often delirious He may continue to complain of headache, usually has marked anorexia and frequently nausea To be sure, some of these symptoms are toxic manifestations of the drug The physical signs of pneumonia may continue to develop or may be abruptly aborted

The most striking feature of the response is the consistency with

which the blood cultures in bacteremic cases become negative following sulfapyridine. This usually occurs even in cases of overwhelming blood stream infection. In our New York and Bellevue Hospital series, only four out of sixty bacteremic cases had positive blood cultures following the institution of sulfapyridine therapy. One of these had a definite endocarditis and another a meningitis and suspected endocarditis. The most miraculous recoveries following sulfapyridine are those that have occurred in the bacteremic cases with high colony counts. Two of our type V pneumonias recovered, both late cases, with blood-culture plates showing innumerable colonies (over 1,000 per cc.). One of these patients had sulfapyridine and serum and the other had sulfapyridine alone. A type III patient with 250 organisms per cc. in the blood recovered from his pneumonia, although he died many months later following surgical treatment of a lung abscess. Graham and his associates in Toronto described a type III pneumonia with 450 organisms per cc. that promptly recovered after sulfapyridine alone. In pneumococcus bacteremia, it must be admitted that specific serum, even type I, has not shown the dramatic result produced by sulfapyridine.

The effect of sulfapyridine on the incidence and the course of other complications of pneumonia cannot yet be ascertained. However, a few significant observations have already been recorded. Pneumococcus meningitis complicating pneumonia, hitherto almost universally fatal, has been found to respond to sulfapyridine or similar drugs in a few cases. Hodes and his associates have reported one such recovery. Endocarditis, fortunately a rare complication, occurred only once in our sulfapyridine series. The blood could not be kept sterile in this case, even when high blood levels were obtained, and the patient died having developed meningitis also. Empyema has been encountered a number of times, but whether its incidence or course is significantly affected by sulfapyridine remains a moot question. The fact that the prognosis in empyema is so much more serious when it occurs during the height of the pneumonia when the more generalized pneumococcus infection is still active, and that these active infections are so definitely aided by the drug, would indicate that empyema as a whole would be benefited by this treatment. Furthermore, the mortality rate in our own and the reported cases of empyema is unusually low, but the series is not large enough to give significance to conclusions that might be drawn from it.

Secondary infections have been recognized more frequently since

we have been using chemotherapy. For example, a patient with type III pneumonia and bacteriemia, later showed *Streptococcus viridans* and then *staphylococcus* in the blood, but he eventually recovered. In several cases of pleural effusion following pneumonia, *Streptococcus viridans* has been cultured from the fluid. Lung abscess, which is probably a secondary infection, has been encountered several times. It is quite likely that in the future we will see sequelae of pneumonia and pneumococcus bacteriemia that we have not seen in the past—the sequelae that will occur in that group of patients who formerly would have died. Furthermore, there is the supposition that in individuals of a high bacterial susceptibility, while we arrest the primary pneumococcus infection, we do not control the secondary invaders.

Certain of the atypical pneumonias, which in the past have been so difficult to treat, have responded dramatically to sulfapyridine therapy. A particular highlight in our experience of the past year has been that of observing the response in some of the most unfavorable cases of pneumonia complicating heart disease and occurring in elderly individuals. We have had striking recoveries in pneumonias complicating bronchiectasis and asthmatic bronchitis and emphysema. Recently, Hinshaw reported enthusiastically on the treatment of postoperative pneumonia at the Mayo Clinic with sulfapyridine. A number of articles have appeared on the chemotherapy of childhood pneumonia, indicating a lower mortality, fewer complications, and a more prompt recovery.

Undoubtedly, there are forms of acute pneumonia that do not respond to sulfapyridine. The group of atypical pneumonias, variously designated as virus pneumonias or atypical pneumonitis can probably best be diagnosed by a failure to respond to sulfapyridine or related drugs. In our very limited experience, the course of tuberculous pneumonia or tuberculous pleurisy with effusion is not altered by sulfapyridine. It does, however, have a wide scope of action in the common pyogenic infections, and among the different types of pneumococcus there seems to be no variation in effect. On the other hand, occasionally a strain of pneumococcus, regardless of type, may be found to be sulfapyridine resistant. Up to the present time, sulfapyridine-fastness has been demonstrated clinically infrequently, and most of the deaths have occurred in instances of serious systemic disorder, inadequate therapy, or overwhelming infection at the start of treatment.

The dosage of sulfapyridine remains empiric. No definite correla-

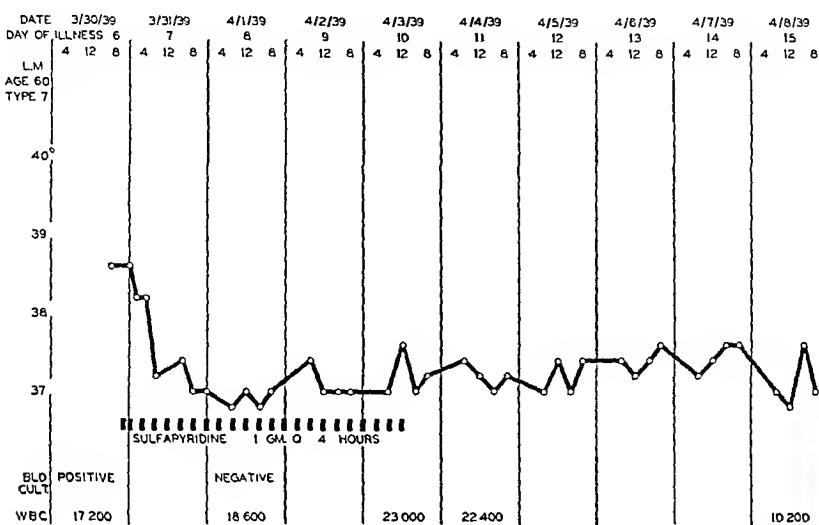
tion between the dosage or the blood level of sulfapyridine and the clinical response has been ascertained. Some of the most prompt recoveries have occurred with a small total dosage and with low blood level readings. At Bellevue Hospital we are continuing to use the dosage recommended by Evans and Gaisford in their original article, i.e., 2 gm as an initial dose, followed by 1 gm every four hours. Sixteen grams suffice for most of the uncomplicated cases. Some investigators have used a higher initial dose and some have given a much larger total amount. Our impression is that the response is no better with the larger dosage, and the patients seem to tolerate the drug more satisfactorily when the blood level is increased less abruptly. Furthermore, the impression is obtained from going over reports, that the incidence of the serious toxic reactions is higher in the series treated with the larger dosage.

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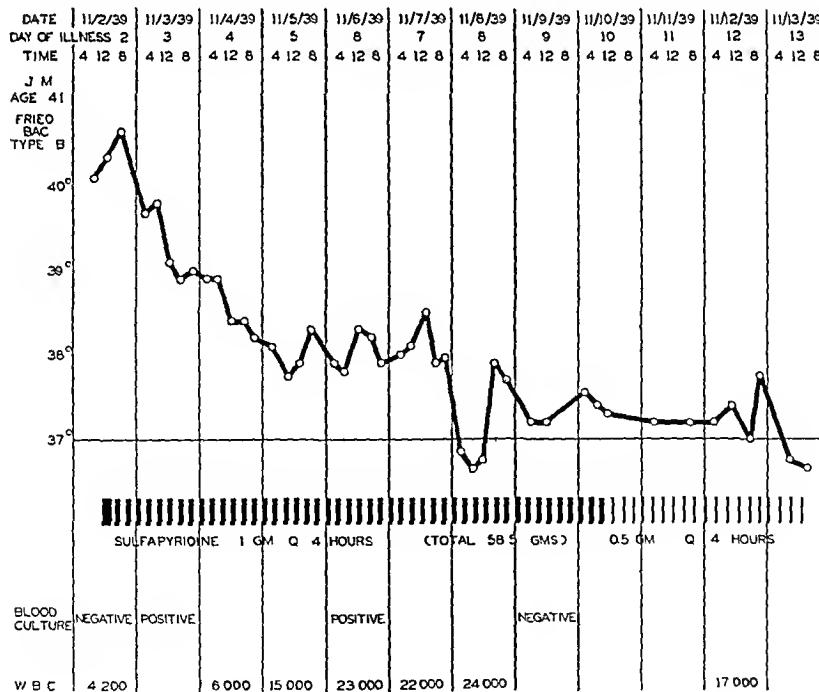
#### LEGENDS FOR CHARTS

Chart I This is the temperature curve of a 60 year old female patient admitted to New York Hospital on the sixth day of her illness. She had had fever, cough, and rusty sputum for 6 days and had been moderately jaundiced for 2 days. The physical signs and x-ray film showed consolidation of both upper lobes and resolving pneumonia of the right lower lobe. The jaundice was considered to be secondary to the acute pneumonia. The sputum yielded type VII pneumococci. Because of the acuteness and the extent of the pulmonary disease, in spite of the jaundice, sulfapyridine was instituted in the usual dosage shortly after admission. On the day following admission the blood culture was found to be positive. Sulfapyridine was continued until a total of 24 gm had been administered. During this time, the temperature dropped, the blood culture became negative, and the jaundice subsided. The clinical improvement was steady, although the temperature remained low-grade and the white count elevated for several days. Recovery was finally complete. Cholecystograms made during convalescence, proved to be normal.

Chart II This shows the chart of a 41 year old man, who had cirrhosis of the liver and acute Friedlander's bacillus pneumonia of the right upper lobe and part of the right lower lobe. He was given 2 gm of sulfapyridine shortly after admission, and then 1 gm every 4 hours for 9 days, then 0.5 gm every 4 hours for 8 days. A total of 58.5 gm was administered. The admission blood culture was negative, but the blood cultures on the second and fifth days grew type B, Friedlander's bacilli. Later blood cultures were negative. Sulfapyridine was given in the face of known liver disease and severe icterus. There was at first an increase and then a clearing of the icterus, but there was no other evidence of aggravation of the liver condition. During the first seven days of sulfapyridine therapy, the white blood cells increased from 4,200 to 24,000, but the hemoglobin dropped from 82 to 60 per cent. This patient has recovered from the acute pneumonia, but has developed a chronic Friedlander's bacillus abscess of the lung. On postural drainage, the abscess has reduced greatly in size, and at the present time we feel that the ultimate prognosis is quite good.



### CHART I



## CHART II

Sulfapyridine has been administered by mouth in most of our cases. Attempts to give the drug by rectum have failed because the absorption is either very small or absent entirely. Blake and Haviland have dissolved 2 gm of sulfapyridine in 1 liter of 5 per cent dextrose in saline solution by heating the preparation nearly to boiling, and have used this intravenously or by hypodermoclysis. Following Blake's method, the chemists at the Lederle Laboratories have been able to prepare for us a solution of 10 per cent sulfapyridine in 50 per cent glucose. This we have given intravenously, orally, and rectally without any reactions other than would be expected from a given concentration of sulfapyridine in the blood. However, when given rectally, similar to sulfapyridine, there is very slight absorption. When given intravenously, the free sulfapyridine blood content rises immediately to a level of about 2 mg per cent (when 2 gm is given), and falls within an hour to an almost negligible concentration. When given orally, blood levels

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#### LEGENDS FOR CHARTS

Chart III. This shows the chart of a 46 year old man, admitted to New York Hospital a few hours after the onset of acute respiratory symptoms with bloody sputum. Physical examination and x-ray revealed pneumonia of the right lower lobe. The sputum showed type III pneumococci. The blood culture taken on admission was sterile. The urine analysis on admission was normal. Sulfapyridine was started shortly after admission with 2 gm as the initial dose and then 1 gm every four hours. The temperature dropped rapidly and the respiratory symptoms subsided promptly. On the second day after admission, after 11 gm of sulfapyridine had been administered, there was sudden pain in the left side of the abdomen and in the left flank. The urine was found to be grossly bloody. Sulfapyridine was discontinued. On the next day an intravenous pyelogram showed a negative stone in the left kidney. Two days later, cystoscopy revealed numerous small concretions on the floor of the bladder and at the ureteral orifice. The hematuria and pain subsided in three days. Later pyelograms and kidney studies were negative.

Chart IV. This is the chart of a 62 year old man admitted to New York Hospital on the seventh day of acute symptoms of fever, pain in the right chest, and cough. The sputum showed type V pneumococcus. The physical and x-ray findings were those of lobar pneumonia of the right upper lobe and the upper part of the right lower lobe. Sulfapyridine was started on admission. The following day, when the blood culture, taken on admission, showed over 2,000 organisms per cc, serum was administered in large amounts, to a total of 390,000 units. There was marked clinical improvement for several days, but then the temperature rose moderately, although sulfapyridine was continued until the eighth day after admission. On the ninth day empyema was diagnosed. The fluid revealed type V pneumococci. Three thoracenteses were done and on the twentieth day after admission a closed tube drainage was instituted, following which the convalescence was rapid and uneventful. This shows the recovery of a patient treated late in the disease when an overwhelming bacteremia was present. Such a recovery heretofore in our experience had never been observed.

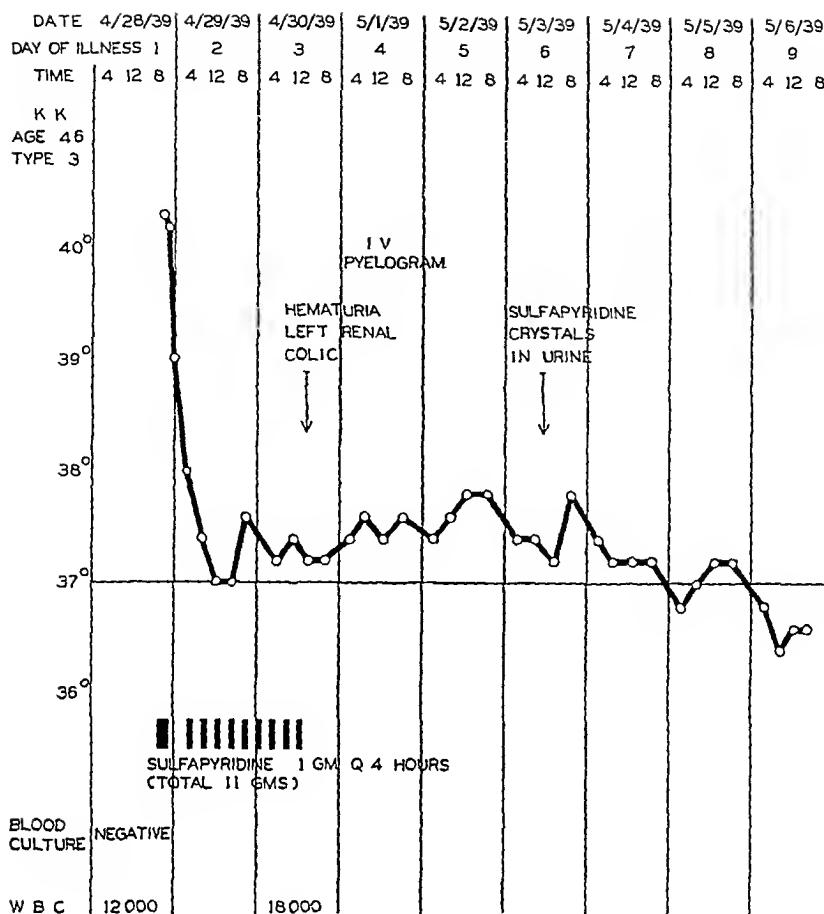


CHART III

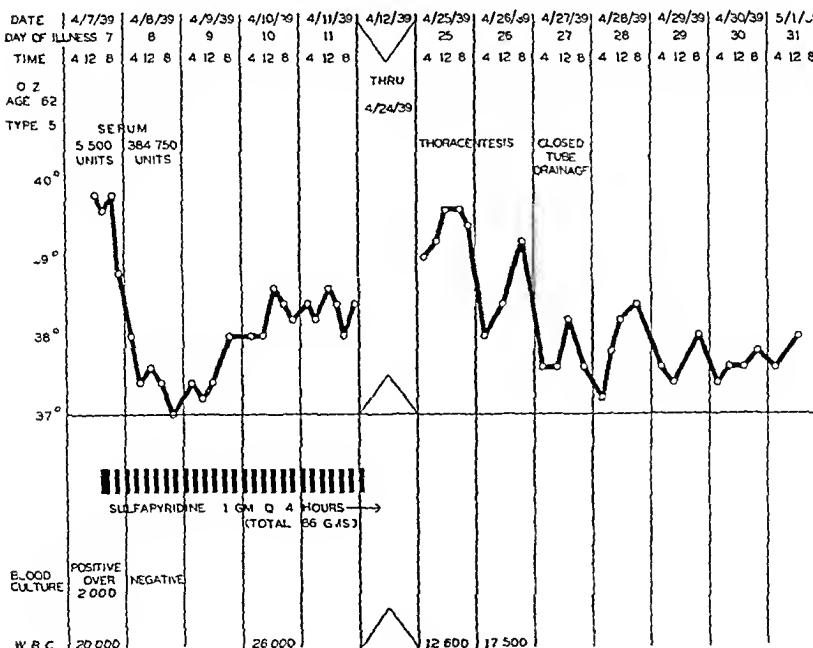


CHART IV

similar to those obtained by giving pure sulfapyridine by the same route, are procured, but the curve rises more slowly, reaching its peak in 24 hours instead of 12 hours. In fifty patients who have been treated with the glucose and sulfapyridine by mouth, using the usual dosage of 2 gm initially and then 1 gm every 4 hours, it is our impression that the same clinical response has occurred with considerably less nausea and vomiting. This finding confirms again our impression that the drug is tolerated better when the level of the blood rises more slowly.

Sodium sulfapyridine has been used intravenously in a few cases when absorption of sulfapyridine from the gastrointestinal tract has been unsatisfactory or when prompt action of the drug has been imperative. Our findings have been in agreement with those reported by Marshall and Long. Also, in a few cases we have confirmed the results reported by Gaisford, Evans, and Whitelaw following the administration of sodium sulfapyridine intramuscularly. Even though sodium sulfapyridine solution is highly alkaline, when given carefully into the deep intramuscular tissue there is only a slight local reaction and the absorption is satisfactory. This mode of treatment, however, is not to be recommended when sulfapyridine can be given by mouth. We have had very little experience in the use of the sodium salt by rectum, but there is mention in the literature that it is regularly absorbed and well tolerated when given this way.

In conclusion, I cannot refrain from making a few remarks regarding the present status of serum in the treatment of pneumonia. It has been shown over and over again that specific serum has value in pneumonia. On the other hand, there are recoveries after sulfapyridine that we would not expect after serum. It is fair to assume that there are some lives that serum will save which sulfapyridine will not. The exact sphere of each of these two agents has not yet been ascertained. Whether a combination of sulfapyridine and serum is a more efficient and more reliable treatment than sulfapyridine alone is an immediate problem for clinical investigation. It seems inevitable that some chemicals will be discovered which are even more effective against disease than sulfapyridine. Charts of four interesting cases are herewith presented.

# A CONSIDERATION OF SOME OF THE TOXIC EFFECTS OF SULFONAMIDE COMPOUNDS, PARTICULARLY SULFAPYRIDINE\*

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**I**T IS axiomatic of pharmacology that drugs are poisons and that the ultimate effect of the reagents is upon the cells of the body. Under controlled conditions, the stimulation or modification of cellular activity may be turned to great advantage in abnormal conditions of sickness. In infections this type of problem is particularly unique since the bacterial cells need to be destroyed but the cells making up bodily structure need to escape destruction. One of the reasons for the limited success of the chemotherapy of bacterial infections has formerly rested upon the fact that the so-called antiseptics were no respectors nor selectors of cells, with the result that the cells of the body were destroyed along with the bacterial cells. Even the relatively more successful kinds of reagents such as those with a mercurial base act through combination with the protoplasmic protein of the cellular structure. These chemicals are, therefore, in a sense, anatomical poisons in that they alter constituents of anatomical structure. Consequently, since proteins constitute such a large percentage of bodily structure, the quantitative extent of union between the types of bactericidal agents, just mentioned, and bacterial protoplasm could not be very effectual in competition with the enormous excess of body protoplasmic protein available for combination with the mercurial compounds.

Without entering into a consideration of the mechanism of the action of reagents of the sulfonamide series it seems highly likely that the effect is through destruction or impairment of some physiological activity of bacteria which is necessary for viability or virulence. Since, therefore, types of cells have individual physiological processes, irrespective of whether they be bacterial or part of the body mosaic, it

\* Presented January 4, 1940 at the Annual Meeting of The New York Academy of Medicine

appears that with the sulfonamide group of drugs an instrument is at hand which has selective possibilities In combating infections the physiological poisons hold great promise as compared to the anatomical poisons The sulfonamide drugs are, however, short of being absolutely ideal because patients receiving the drugs are subject to certain toxic manifestations, although remarkably—and in many instances dramatically—aided in overcoming the infection

The rate of accumulation of literature in such an important subject is so considerable that data collected at one time are liable to be out of date within a very short period For example, the earliest few articles on the treatment of pneumonia with sulfapyridine gave no special consideration to hematuria We have now come to learn that this is a toxic manifestation of possibly greatest importance Conversely, matters of particular early interest, such as effects on hydrogen ion equilibrium and even cyanosis, appear now to be looked upon less seriously It is apparent, therefore, that an attempt at a statistical analysis of the frequency of the several toxic effects would at this time be premature Indeed to attempt to list all the different kinds of reactions is unsatisfactory because, in addition to variations in published reports, innumerable individual personal experiences of physicians have not yet been consolidated into uniform findings

I should like, therefore, to review the general order of magnitude, based on current information, of certain selected toxic effects, to comment on the mechanisms in so far as they are known, and to point out certain individual findings which have not yet received widespread attention but which warrant further inquiry and observation, because of the practical clinical questions which they provoke

Among the drugs containing the sulfonamide configuration there appear to be certain toxic manifestations which are a denominator common to all of them that have been tried up to the present time, and, in addition, there are particular manifestations peculiar to the individual compounds It has always been an interesting fact that the pharmacological action of drugs cannot be regularly predicted on the basis of chemical structure With the increasing number of sulfonamide derivatives which are constantly being presented for clinical use, it becomes necessary to look for individual and unsuspected toxic manifestations as well as the ones already recognized

The actions of sulfapyridine will be the chief subject for this dis-

cussion with appropriate reference to sulfanilamide. Without itemizing all the untoward reactions, the striking toxic effects which I should like to consider, center around the central nervous system, the hematopoietic system, and the urinary tract.

### CENTRAL NERVOUS SYSTEM

Mental disturbances have been noted frequently but have usually been mild in degree, taking the form of confusion, restlessness, dizziness, irritability or lassitude, and, in some instances, hallucinations. The degree and nature of the psychic disorders are not always easily measured because severe acute infections themselves may contribute an element of delirium. So far as I am aware no refractory psychiatric sequelae have persisted after cessation of the drug. The condition constitutes a transient disorder, disappearing when the drug has been eliminated but not yet referable to any arbitrary blood concentration above or below which mental symptoms appear or disappear. Fortunately there seems to be no definite summation of mental symptoms referable to disease plus drug. However, within the realm of cerebration some interesting experimental findings have been recorded concerning the combined effect of the sulfonamides and certain other drugs. Of possible clinical importance are the results reported by Adriani<sup>1</sup> concerning the combined effect of sulfanilamide and some of the anesthetic drugs. The anesthetic action of ether and chloroform was found to be the same in normal animals and in those receiving sulfanilamide. However, when an amount of barbiturates—such as amytal, nembutal and others—necessary to induce anesthesia was administered to rats, if the animals were receiving sulfanilamide, they died, whereas normal controls emerged from the anesthetic state unharmed. Furthermore, an amount of barbiturates which induced only subanesthetic states in normal rats, caused deep anesthesia and in some instances death in animals receiving sulfanilamide. The implications of these findings concerning the selection of the type of anesthetic in surgical patients receiving sulfanilamide are obvious. The question might also be raised concerning the advisability of administering barbiturates for sedative or soporific purposes, although the dosage may be too small to give results comparable to those found in experimental tests with anesthetic doses of barbiturates. Glaubach<sup>2</sup> has reported that the sedative and anesthetic effects of papaverine are augmented by sulfapyridine. When an amount of papaverine, which in normal animals produced a

transient narcotic effect, was given to other animals receiving sulfapyridine deep narcosis resulted and some of the animals died

These findings indicate that the transient psychic reactions noted clinically, although not serious when taken alone, may have a deeper significance when other drugs affecting the higher centers are given simultaneously

### NAUSEA AND VOMITING

With sulfapyridine therapy, nausea and vomiting are by far the commonest toxic effects. In this respect sulfapyridine differs strikingly from sulfanilamide, and this difference illustrates the unpredictability of pharmacological effect when chemical structure is altered, although the sulfonamide grouping remains present in both drugs. The incidence of nausea and vomiting, or both, has been noted by observers in frequencies which usually average over 50 per cent. The nauseous and emetic action is currently believed to be of central origin, the chief factor favoring this interpretation being the fact that the symptoms may arise following parenteral administration of sulfapyridine. However, there appears to be no critical level of blood concentration at which nausea is induced. Furthermore many patients have no difficulty with *mal-de-me* even though the blood concentration is unusually high, and still other patients begin the upset within an hour or two of beginning treatment. It is apparent that there is an individual personal element which is unrelated to an arbitrary physiological reflex set off by a quantitative level of drug. One interesting fact noted by several observers is that the vomiting, if not extreme in degree, may not seriously interfere with the effectiveness of the remedy nor indeed the blood level. If the intact tablets are not ejected very quickly after ingestion, it is surprising how frequently the curative effect and blood concentration are comparable to results noted in patients who do not vomit.

As with the other untoward reactions so far mentioned, no serious results or persistent after-effects of the emetic action have been noted with the exception of those referable to disarrangement of fluids and electrolytes due to vomiting—conditions which are amenable to adjustment by parenteral replacement—and of those referable to the strain on abdominal wounds and surgical incisions in postoperative pneumonia.

In connection with problems in sulfonamide therapy which are of special interest to surgeons, the report of Bricker and Evarts Graham<sup>3</sup>

may be of interest Using dogs in an experimental study they found that the tensile strength of a recent incision in the wall of the stomach was less in dogs which were receiving sulfanilamide than in normal animals They noted that this tensile strength of the wound in sulfanilamide treated animals was weakest very early after the repair process began and that the difference between normal and treated animals was less significant the longer after the operation the tests were made These findings suggest that fibroblasts may be particularly susceptible to impairment by sulfonamides, an untoward reaction which might occur in some other types of embryonal cells, as in the immature cells of the bone marrow

#### HEMATOPOIETIC SYSTEM

Of more importance than the transient and almost uniformly harmless toxic manifestation just mentioned, is the damaging effect upon the blood cells and blood-cell-forming organs This occurrence may assume serious proportions and constitutes the chief cause of fatality following sulfonamide therapy Among the published reports of cases treated with sulfapyridine, six deaths have been directly attributable to the action of the drug on the blood-forming organs With sulfanilamide there are a somewhat larger number of reported fatalities However, in either case, the numbers are very small in proportion to total number of treatments Non-fatal cases with alterations in blood cells have also been observed of mild, moderate and severe degrees The granulocytes rather than the lymphocytes suffer the greatest damage In the fatal cases, the white blood-cell-forming marrow suffers from a damage which is irreversible even though administration of the drug is stopped When a drop in the number of white blood cells sets in, there is at present no way of determining whether the granulocytopenic effect will cease when therapy is stopped or will proceed to a fatal outcome

We have had the opportunity to observe in a few instances unusually transient effect of the drugs on white blood cells One instance will illustrate the point The patient had gonococcal arthritis and was treated with sulfanilamide She developed some toxic manifestations and the drug was stopped At a later date when conditions had reached normal equilibrium, she was given a gram of sulfanilamide and blood counts were done at two-hourly intervals for most of the ensuing twenty-four hours Her count steadily rose for about fifteen hours until it doubled

itself, then dropped quickly again so that by twenty-four hours it was at the same level as at the beginning. In this case daily determinations of the number of white blood cells after the single dose would have failed to reveal the episode of transient irritation. Findings such as this also suggest that minimal effects may occur more frequently than is ordinarily suspected.

The question of individual idiosyncrasy which this patient also illustrated is an interesting one. The frequency with which the same individual responds with the same toxic reaction has not been settled. That it occurs in some instances is clear. The question may also be posed but not answered, whether individuals who react unfavorably to sulfonamides may have a broad idiosyncrasy to drugs such as amidopyrine and others.

When the red blood-cell system is chiefly affected the manifestations appear as an acute hemolytic anemia, or as a secondary anemia which develops with varying degrees of rapidity and severity. The acute hemolytic phenomenon is characterized by destruction of half or even more of the circulating red blood cells within a day or two. Irritation of white blood-cell-forming organs accompanies the event and is manifested by an unusually high leukocytosis. The hemolytic crisis appears to occur somewhat less frequently with sulfapyridine than with sulfanilamide.

In addition to the acute incident, secondary anemias, which gradually develop over days or weeks, have been noted, in which red blood cells and hemoglobin may drop to varying levels as low as half of normal only to return uneventfully to normal following cessation of the drug.

On the basis of the present limited knowledge, the findings suggest that the toxic effect on the white blood cells is most frequently reflected by damage exerted at the source, namely the bone marrow, where immature early forms of cells are present, whereas with red blood cells the mature circulating forms are particularly vulnerable to destruction.

#### URINARY TRACT

Perhaps the most significant effect of sulfapyridine, which is not shared to the same degree by sulfanilamide, concerns the toxicity manifested by abnormalities in the urinary tract. Clinically, these are hematuria, calculus formation and nephritis.

The rapidity of the renal excretion of sulfanilamide and sulfapyri-

dine is one of the striking characteristics of the drugs. The mode of excretion is also of interest. Marshall and associates<sup>4</sup> have found that they are eliminated by glomerular filtration and that reabsorption to the extent of 80 per cent occurs in the tubules, a procedure similar to that by which urea is handled in the kidney. This indicates that the tissues of the glomeruli and the tubules are exposed to whatever effects the drugs may exert while transferring either from blood to lumen of the tubules or from lumen back to blood.

It has also been made clear that sulfanilamide and to a greater extent sulfapyridine undergo chemical alterations in the body, one of which is acetylation. This particular change in chemical constitution results in a compound which is poorly soluble and therefore crystallizes readily out of solution. It appears, therefore, that the crystalline form is the source of the damage. The crystals in all probability scratch the lining of the tubules, pelvis and ureters as they progress down the urinary tract. The hematuria is therefore in the nature of mechanical trauma rather than a chemically poisonous effect on the renal cells. When the crystals of acetylated compounds accumulate in sufficient numbers, a calculus is formed, which in itself may reach a size sufficiently large to give all the signs and symptoms of renal colic. Finally nephritis with nitrogen retention and renal insufficiency appears also to be based on this mechanical circumstance, with dilated pelvis, damping back of urine, enlargement of kidney and renal insufficiency. The matter may be further complicated by the fact that above the point of stasis infection may be introduced with pyelitis and pyelonephritis developing. Whether or not primary acute glomerular or tubular nephritis occurs, which is dependent upon damage exerted by the drug in its passage from blood to lumen in filtration or from lumen back to blood in reabsorption, has not been clearly determined. Such a possibility is a reasonable one. McLeod<sup>5</sup> has reported two patients who developed renal insufficiency without hematuria and might fall into this category.

The occurrence of hematuria from the standpoint of frequency is difficult to assay from the literature. As was previously brought out, the earliest reports of cases treated with sulfapyridine did not mention hematuria. This finding has been a matter of special interest in recent reports. Such successive increases in per cent occurrences as 2 per cent, 18 per cent and 25 per cent are noted. It occurs in both children and adults. It occurs at times when the urine is alkaline as well as acid, the insolubility

of acetyl sulfapyridine persisting through wide ranges of pH. It clears up in a few days after treatment is stopped, with certain exceptions that will be subsequently mentioned. One point of interest which may be culled from cases cited in several publications is that patients who developed hematuria at the time of the first administration of sulfapyridine have, at a later period when the drug was given again, developed hematuria again. The individuality of the idiosyncrasy appears on occasion to be applicable to the renal toxic effect as well as in the hematopoietic one. The development of calculi is clearly an authentic occurrence, which has been produced experimentally in several different species of animals<sup>6</sup> and has been observed in treated patients both clinically with the signs and symptoms of renal lithiasis<sup>7</sup> and pathologically by the demonstration of the stones with assay of their chemical constitution.

Nephritis with renal insufficiency constitutes the most serious complication of those involving the urinary tract. Fortunately the incidence is small and I have not found reference to a death due to nephritis, per se. However, what the future outcome may be for persons who have once had functional impairment of the kidneys remains to be determined. Indeed, the eventual prognosis is a question which deserves consideration in the cases in which transient hematuria is the only manifestation of damage to the urinary tract.

In the present state of knowledge, it may be stated that the abnormal appearance of red blood cells in the urine in quantities which vary from a few identified microscopically to gross hematuria is a common but transient occurrence, the exact frequency of which has not been established, that crystals of acetyl sulfapyridine may be identified in the urine either chemically or microscopically, or often may be seen with the naked eye as points of light refraction, that when the crystals agglutinate in sufficient numbers, the problem of renal lithiasis is presented, finally, that nephritis with renal insufficiency may develop. Fortunately, from the standpoint of an immediate reaction, the frequency of these effects and their seriousness appear to bear the relation of inverse proportion, hematuria being the mildest and commonest, nephritis being the most serious but considerably less frequent.

The toxic manifestations which have been emphasized in this discussion have been selected topics which are not inclusive because of the limitations of time. Even from those mentioned it is apparent that sulfonamide drugs are not entirely perfect in the job of promoting the

destruction of bacterial cells while leaving the cells of the body completely unaffected. But it is also clear that the life-saving effectiveness of sulfanilamide and sulfapyridine outweigh the immediate toxic reactions.

In considering these drugs, by way of brief recapitulation, two points, among many, may be selected for restatement. First, what is the combined action of the sulfonamides plus other reagents of either chemical or biological origin with respect to augmenting, supplementing, altering, or inactivating effects on the body? That sulfanilamide and sulfapyridine undergo and induce chemical changes in the body is clearly indicated by acetylation, by esterification, by effects on metabolism such as is reflected in the excretion of porphyrin, and by some as yet unexplained reaction involving oxidation-reduction processes, the most striking manifestation of which is the formation of methemoglobin. What other chemical reactions may occur with what other reagents and lead to what other kind of toxic effects are problems which remain to be determined. From a practical current clinical point of view these unknown circumstances emphasize the importance of judiciously considering the selection of accessory drugs that may be given simultaneously with the sulfonamides. A second unsettled point concerns the effects which may become evident a considerable time after the drugs have been given. The most obvious hazard in this respect is the initiation by crystals of acetylated sulfapyridine of calculus formation. It is not unreasonable to consider the possibility that a nucleus might be established around which and on which mineral salts may be gradually deposited over a period of months or years until the disorder of kidney stone becomes established. It is perhaps also important to contemplate what significance may be attached to the transient abnormalities, which are evident during the period of drug administration but which seem to disappear when therapy is stopped. Is there a residue, for example, of renal impairment or bone-marrow impairment which is so minimal as not to be evident when the patient has recovered but which will eventually add up to a sufficient degree to cause some chronic disease, if repeated over a number of years either with repetition of sulfonamide therapy or other therapies which induce similar damages? If the healing of the body cells intoxicated by the drugs is complete, the incident is a closed one. If damage to some of the body cells is permanent, even if minimal, the summation effect of repeated insidious damage may, when

and if it occurs, eventually be a serious matter. Without implying unwarranted concern for remarkable remedies, the problem justifies detailed observations over a period of years before the seeming harmlessness can in all respects be finally appraised.

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## HYPERPITUITARISM AND HYPOPITUITARISM\*

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## INTRODUCTION

THE pituitary gland, in the words of Harvey Cushing,<sup>1</sup> "exercises direct or indirect control over an unsuspected number of biochemical processes of utmost importance to the economy of the body." There are, for this reason, undoubtedly innumerable states, some pathological, others bordering upon the pathological, in which dysfunction of the pituitary gland is involved. However, our present state of knowledge of pituitary dysfunction without demonstrable morphologic changes in the pituitary gland is such that it is dangerous speculation to attempt to ascribe many bizarre conditions, as claimed by uncontrolled and popular endocrinology, to improper secretion of the pituitary gland.

Indeed, there must be a considerable margin of safety in the quantity of functioning glandular tissue of the anterior lobe of the pituitary body since one not infrequently sees patients with partial destruction of this organ by tuberculosis, syphilis or embolic phenomena without any detectable symptoms ascribable to loss of pituitary secretion.

However, sufficient experimental data and clinical and pathological evidence exist to make possible the recognition of two important classes of pituitary disturbances, namely, hyperactivity and hypofunction of this gland.

Of all the verified diseases of the pituitary gland producing one or the other of these groups of symptoms, the commonest is the adenomatous tumor.<sup>2</sup> The type of clinical response to such a tumor varies with the type of cell from which the tumor arises.

## HYPERPITUITARISM

## ACROMEGALY

*Definition* Acromegaly is a disease which is characterized by a specific type of pituitary adenoma and an overgrowth of the terminal, thus acral, parts of the skeleton such as the nose, mandible, hands and feet.

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*History* Pierre Marie,<sup>3</sup> in 1886, is generally accredited with having described this disease. Certainly he gave it its name and presented the first clinical picture of it as a disease entity by the report of two cases. The etiology of the disease was, however, very much in doubt for another fourteen years.<sup>4</sup> The pituitary gland was somehow believed to be involved, but Marie himself thought for a long time that the disease was an expression of underfunction or at least dysfunction of the gland. In 1900, Benda<sup>5</sup> conclusively demonstrated that the pituitary lesion with which acromegaly was associated was an adenoma consisting of cells containing eosinophilic granules, that these granule-bearing cells were similar to those which are present in large numbers during the growth period in normal individuals and that acromegaly was in all probability a result of hyperactivity of the pituitary gland.

In 1909, Cushing<sup>6</sup> was able to demonstrate experimentally that pituitary extirpation retarded skeletal development, and thus inferred that the skeletal hyperplasia, occurring in acromegaly and the related condition, gigantism, was due to hyperactivity of the gland. H. M. Evans<sup>7</sup> (1923) was able to produce gigantism in rats by repeated injections of extracts from the anterior lobes of beef pituitaries, and Putnam<sup>8</sup> (1928), experimental acromegaly in dogs by a similar method.

*Etiology* Acromegaly is a rare disease. There are five times as many cases of pituitary tumors of the chromophobe type without acromegaly as chromophile tumors with it. It can occur in all races, and affects both sexes about equally. The disease has its onset at a relatively early age (average about 26 years) but because of its chronic character patients are often first observed past middle life.

Frequently acromegalic patients give a history of notably large kinsmen, and occasionally even of acromegaly in a near relative, but the disease cannot be considered primarily as a familial one.

*Morbid Anatomy* The primary lesion in acromegaly is an adenoma of the anterior lobe of the pituitary body consisting of cells, the cytoplasm of which contains granules staining specifically with eosin and other acid dyes.<sup>9</sup> This lesion not only results in an enlargement and deformity of the pituitary gland and consequently of the sella turcica, but because of its oversecretion of hormone, resembling most perhaps the growth-promoting hormone, it produces secondary effects upon practically every tissue and organ in the body.<sup>10</sup> These secondary effects may be divided into two groups namely, those exerted upon the neighboring

structures of the tumor by the mechanical pressure of the growth, and those exerted upon distant structures by the hormonal influence of its secretions

The first results in atrophy and enlargement of the sella turcica, pressure atrophy of the optic nerves and chiasm, irritation or atrophy of the hypothalamic portion of the floor of the third cerebral ventricle, occasionally, atrophy of some degree of the olfactory tracts and nerves

The most conspicuous hormonal effect of the lesion is upon the skeleton. When the onset of the disease is early in life before the closure of the epiphyses, the stature of the patient may increase to gigantic proportions. Authenticated cases of patients attaining a height of eight feet (240 cm.) exist in the literature. These patients, although large, may be symmetrically developed without deformities and are said to suffer from gigantism rather than acromegaly. Most frequently, however, the giants show, in addition to their great height, an undershot jaw (prognathism) and great hands and feet out of all proportion even to their own unusual size, thus approximating the usual type of acromegaly. In addition to the prognathic jaw, the head also shows as a rule a great thickening of the calvarium and an enlargement of the air sinuses. The vertebral bodies and the points of attachment of the muscles and tendons to the bones frequently show marked hyperostoses. The spinal column often shows a fairly marked general kyphosis, the ribs become heavy and the chest cage resembles a great barrel.

In addition to the bone-changes, the nerves, blood vessels, skin, glands, and fat reveal generalized hypertrophy, but this is particularly true of the connective tissue throughout the body. While much of this hypertrophy is due to actual increase in the number of cells and the quantity of intercellular substance, a certain amount is also ascribable to a peculiar edema of the subcutaneous tissues which is moderately mobile and is the first to disappear if the secretion of the adenoma can be diminished by surgical or roentgenologic means.

Less obvious than the enlarged acral portions but equally striking is the generalized splanchnomegaly occurring in this disease. This affects not only the viscera but, to a special degree and in a special sense, the other endocrine organs such as the thyroid, thymus, parathyroids and adrenal glands which are often the seat of adenomatous lesions, so that this disease is sometimes referred to as multiple adenomatosis.

*Symptoms* The distinction between symptoms and signs in acromeg-

TABLE I

## SYMPTOMS AND SIGNS OF ACROMEGALY AS RECORDED IN CLINICAL HISTORIES

<i>Symptoms and Signs</i>	<i>Incidence (Per Cent)</i>
Enlargement of acral parts	100
Enlargement of sella turcica on x-ray examination	93
Disturbances of menstrual cycle	87
Headache	87
Complete amenorrhea	73
Increased basal metabolic rate	70
Visual disturbances	62
Excessive perspiration	60
Hypertrichosis	53
Cutaneous pigmentation	46
Drowsiness and lethargy	42
Gain in weight	39
Diminished libido sexualis	38
Asthenia	33
Low blood pressure (less than 120 mm Hg systolic)	30
Paresthesia	30
Polyphagia	28
Fibromatous mollusci of skin	27
Polydipsia	25
Enlarged thyroid gland	25
Glycosuria (diabetes mellitus 12)	25
Constipation	25
Vomiting	16
Rhinorrhea	15
Photophobia	12
Uncinate attacks	7
Failing memory	7
Decrease of body hair	7
Persistent lactation	4
Failure of breasts to develop	4
Epistaxis	3
Choked discs	3

galy is particularly difficult since many elements belong to both categories. The disease, as may already be suspected from the description of the varied pathological manifestations, is extremely protean<sup>11</sup> and the enumeration of the symptoms and signs in Table I makes a formidable list.

Time will not permit me to discuss more than a few of these in detail.

*Acral Overgrowth.* The peculiar overgrowth of the hands, feet and features is of necessity present to some extent in every case, since the clinical diagnosis and the name of the disease is based on the presence of these manifestations. A closer investigation of the acromegalic patient reveals that the overgrowth is general and not confined to the extremi-

ties. The changes in the latter, however, call attention to the disease. The hands and feet become much enlarged, but especially in width and thickness and the first inkling of this change may come to the sufferer through the need of frequently increasing the size of his gloves and shoes. The skin becomes thickened and the joints of the fingers and toes become relaxed, the pores are coarsened and perspiration increases so that one gains the impression in grasping the hand of an acromegalic that it consists of a moist, relaxed sac incompletely filled with loose bones. The nose becomes wide and large, the lips and brows thicken, the spaces between the teeth increase, owing to the enlargement of the jaws, and the lower jaw becomes prognathic because of its relatively even greater hypertrophy than its fellow. The tongue hypertrophies so that it overfills the cavernous mouth and the speech grows lisping and indistinct.

If the onset of the disease occurs before the closure of the epiphyses, the entire stature increases beyond normal and may reach gigantic proportions. The circumference of the chest becomes greatly augmented. Sooner or later a "rounding" of the shoulders occurs due to hypertrophic changes in the vertebrae.

*Menstrual Changes* In the majority of female patients, oligomenorrhea or amenorrhea appears early in the disease. This symptom is associated with sterility since impregnation in an acromegalic woman practically never occurs after the onset of amenorrhea, although acromegalic women can bear children if their menses continue. The interruption of ovarian function seems at first incompatible with the fact that in cases of chromophobe adenoma of the anterior lobe of the pituitary, which present in every other respect a directly antithetical picture, amenorrhea and sterility are also produced. Henderson<sup>12</sup> has shown, however, that the onset of this symptom in either type of adenoma is related to the size of the tumor, and comes about when this has attained such a size as to interfere with the sex stimulating hormone of the normal part of the anterior lobe.

*Headache* is present in nearly 90 per cent of acromegalic patients who apply for treatment to the neurologist and more especially neurological surgeon. This symptom is due, it is believed, to the stretch put upon the dural diaphragm across the sella turcica by the expanding tumor within it.

*Visual Disturbances* These consist of symmetrically disposed visual field defects in the temporal halves of the fields which progress until the

typical bitemporal hemianopia is produced, and which, if untreated, may go on to complete loss of vision. The cause of these changes is the pressure of the tumescent gland against the optic chiasm. If the tumor is allowed to grow beyond this point, it may break through its capsule and extend into the cranial cavity. When this occurs, the growth is usually asymmetrical and the visual field defect may change correspondingly. Rarely one even sees papilledema with a pituitary adenoma as a result of intracranial extension and increased intracranial pressure. The usual picture of the eyegrounds is one of primary atrophy of the optic discs.

*Complications.* The complications in the course of this disease are practically all due to the advancement of the above symptoms to their final stages.

*Blindness* may result if the growth of the adenoma continues and is not checked either by operation or roentgenotherapy.

*Increased intracranial pressure* may occur if the tumor breaks through the confines of its capsule and all its accompanying symptoms may appear.

*Diabetes mellitus* is a common complication, and though it does not run a course similar to the essential type of diabetes, nevertheless, it may end in diabetic coma.

*Increased basal metabolic rate* is frequent in acromegaly and sometimes this reaches a state analogous to thyroid toxicosis. Resection of the thyroid usually improves this condition, although histologically the thyroid shows the picture of a colloid goiter instead of that of hyperthyroidism.

*Asthenia and low blood pressure* may occur.

*Arteriosclerosis and myocarditis* are more common and occur at an earlier age than would be expected in normal individuals.

*Diagnosis.* The diagnosis of acromegaly (pituitary acidophilism) is the simplest thing about the disease. The coarse features and especially the prognathic jaw, the huge hands and sausage-like fingers, the great feet, barrel chest, rounded shoulders and ape-like carriage, make the diagnosis possible literally at a distance. When the disease begins very early in life, however, the stature may be abnormally great but the acral portions, though large, are as a rule more shapely, and in proportion to the rest of the body. While severe acromegaly can exist with an adenoma so small that the sella turcica is not expanded, in the majority of cases the tumor enlarges the gland enough to give some visual field defects.

and changes in the sella turcica sufficient to be visible in roentgenograms of the skull

The Roentgen films of the skull in acromegaly characteristically show thickening of the calvarium, ballooning out of the frontal sinuses, prognathism and a sella turcica which is enlarged to greater or less degree, often with depression of the sellar floor and thinning or erosion or even complete destruction of the anterior and posterior clinoid processes and the dorsum sellae. The terminal phalanges of the fingers and toes show a peculiar "tufting" on the roentgenogram, which is quite characteristic of the disease, and the rest of the skeleton presents a massiveness which is easily recognizable.

*Prognosis* Acromegaly is a chronic disease which may last as many as forty years in an attenuated form. Often the adenoma degenerates or loses its secretory qualities and the patient may go into a state of hypopituitarism due not only to a "burning out" of the adenoma but also to the destruction of the normal pituitary gland. However, whether sufficient of the normal pituitary gland remains or not, and even when the adenoma ceases functioning altogether, the skeletal changes do not recede, so that the patient's appearance is always that of an acromegalic. Frequently the growth of the adenoma and its secretory capacity continue unabated and unless treated, produce blindness, intolerable headaches, and the various other complications until death ensues.

*Treatment* Since the basic pathological lesion in acromegaly is the acidophilic adenoma of the pituitary gland, treatment, in order to be fundamental, must be applied directly to this growth. This may be done either by surgical or roentgenological methods or a combination of both. The acidophilic adenoma of acromegaly is radiosensitive in about 60 to 70 per cent of cases. If the patient presents himself sufficiently early, before his visual power is threatened, radiotherapy should be tried. If the vision is in imminent danger, a partial surgical extirpation of the tumor should be made and roentgenotherapy applied postoperatively to devitalize the remainder of the growth.

The most modern surgical procedure consists of a right transfrontal craniotomy, carried out under local anesthesia with an attack upon the tumor between the legs of the optic chiasm, through the bulging sellar dural diaphragm, which has first been incised.

The Roentgen-ray treatment is delivered through three portals, one on each temple and one in the midfrontal region, of 5 x 5 cm. Through

each of these portals, 800 r units are delivered in divided doses of 200 to 300 r units per treatment given daily or every other day. The physical factors in the set-up depend, of course, on the facilities available. As a working method, the following factors may be used:

Kilovolts	200
Milliamperes	8
Screening	(1 mm Al (0.5 mm Cu)
Distance (target to skin)	50 cm
r per minute	20

### PITUITARY BASOPHILISM

*Definition* Pituitary basophilism is a condition chiefly affecting women, and associated with an adenoma of the anterior lobe of the pituitary gland consisting of cells with basophilic granules in their cytoplasm. This point is still controversial and may have to include certain cases without adenomas but in which the basophilic cells of the anterior lobe show certain hyaline changes first described by Crooke in 1935. Clinically it presents a syndrome of painful obesity, hypertrichosis, amenorrhea, with overdevelopment of secondary sex characteristics, plethora, vascular hypertension, purplish striae of the skin, osteomalacia, and a number of other more variable signs and symptoms.

*History* In 1903, Erdheim described the postmortem findings in two cases which showed, on careful histological examination of the pituitary, small adenomas 1.5 mm and 1 mm in diameter respectively, consisting of basophilic granule-bearing cells. He considered these incidental findings, in the nature of histological curiosities, and placed no clinical significance upon them. One of these patients, during life, was considered to be suffering from Basedow's disease, and the other was an acromegalic who showed a large acidophilic adenoma of the pituitary in addition to the tiny basophilic one.

In 1912, in his well-known monograph on "The Pituitary Body and Its Disorders," Harvey Cushing<sup>1</sup> described a "polyglandular" syndrome, in a young woman of twenty-three, which he defined as "a syndrome of painful obesity, hypertrichosis and amenorrhea with overdevelopment of secondary sex characteristics," without being able to attribute the picture primarily to the pituitary, adrenal, pineal or ovary. This patient was seen by him from time to time for over twenty years.

Meanwhile six other similar cases appeared under his observation, and a number of these "polyglandular" cases began to appear in the literature, a few of which were reported together with complete postmortem examinations. One of the most complete reports was by Parkes Weber<sup>13</sup> (1926) in whose patient, among other pathological changes, was found a small pituitary basophilic adenoma to which he ascribed very little significance. Meanwhile, biological evidence of multiple hormones of the anterior pituitary gland was being disclosed and a young co-worker of Cushing, Harold Teel<sup>14</sup> (1931), postulated the presence of a basophilic adenoma in an obese, hirsute woman who also showed menstrual irregularities, and at whose necropsy such a lesion was found.

A search of the literature revealed a number of similar cases, some of which occurred also in males, and in 1932, Cushing's paper<sup>15</sup> appeared with a full review of all reported cases and a number of his own. One of these was that of a man who showed this syndrome to an advanced degree, and in whom a basophilic adenoma of the pituitary was postulated. He improved remarkably after radiation therapy confined to the pituitary region. This seemed to indicate that the lesion primarily responsible was located in the pituitary gland. What that lesion was, as yet was not verified. Later on, however, the patient had a recurrence of symptoms and died before he could be brought back to Cushing's care. Necropsy revealed the presence of a basophilic adenoma of the pituitary gland and the last link in the chain seemed to have been forged to establish the syndrome of pituitary basophilism.

*Morbid anatomy.* Most of the postmortem examinations in those examples of this disease which are recorded in the literature were made before Cushing linked the syndrome to the basophilic adenoma of the pituitary gland. Since this tumor is usually small, often no more than a few millimeters in diameter, it undoubtedly was occasionally overlooked when no special effort was made to find it. As an example, a case reported by Bauer<sup>16</sup> was examined at necropsy by Sternberg, whose report of the pituitary gland was that it was of normal size without change. After the case was published, at the request of Cushing, Sternberg cut the pituitary gland serially and found a small, but typical, papillary basophilic adenoma. It is this lesion, then, which is believed to be the basically underlying pathological cause for the disease.

The other members of the endocrine series are also involved to a greater or less degree. The adrenals often show adenomatous formations

or hyperplasia of the cortex, although normal adrenals have been described in typical examples of the disease. The thyroid is usually normal in size or slightly enlarged. Occasionally a small struma may be present which histologically proves to be colloidal in character. The thymus has usually been reported as atrophied although, in Teel's case, it was found to be persistent. No uniform changes have been seen in the pancreas or pineal. From the few reports on the condition of the parathyroids, it would seem that these bodies are hypoplastic in this disease. The gonads are usually atrophic.

The other tissues and organs show varying degrees of change. The blood vessels are often sclerotic, in spite of the relative youthfulness of the subjects. The heart, as a rule, shows considerable hypertrophy, not in the massive sense as seen in acromegaly, but compatible with a state of chronic hypertension. The kidneys almost consistently show chronic nephritis. The liver may show fatty degeneration, although no detailed studies are reported in the literature.

*Symptoms.* Until many more case reports appear, now that the nature of the disease is better known, the complete clinical picture will have to remain uncertain. In many of the case reports that are extant, the histories are often very much condensed and the chronological appearance of symptoms incompletely noted. In so far as it is possible to determine, the cessation of menses is usually the first symptom in women, unless the disease appears before puberty. In the male patients, obesity is the first indication of the disease. Headache is common, pain is frequently present, especially in the back. The women note, fairly early in the disease, a thinning of the hair on the head and the appearance of body and facial hirsutes. Shortness of breath and palpitation, general weakness, purpuric eruptions are frequently reported. Loss of height, associated with cervicothoracic kyphosis, was observed subjectively in five out of sixteen cases analyzed. Less frequently, exophthalmos, diplopia, nausea, vomiting, epistaxis, tinnitus, dry skin, insomnia or somnolence is noted by the patients.

Objectively the appearance of these patients is as striking in its way as that of the acromegalics. The female victims show a definite growth of hair on the face, although the hair on the head may become thinned. All the patients have strikingly prominent abdomens, suggesting in appearance that of the later months of pregnancy. The obesity extends to the rest of the torso, breasts, neck and jowls. The skin is often

stretched very tightly over these localized areas of obesity and gives the patient a painful feeling as if it were about to burst. On palpation, too, the fat pads are often tender. Contrasted to the obese body and neck, the extremities are usually thin, even wasted. The face is plethoric, the eyes may be prominent and the conjunctivae injected. Purpuric spots are frequently present. Owing to the stretching of the skin, striae are usually present and characteristically appear purple, red or brown. These may be very prominent over the abdomen, thighs, breasts and even axillae. The skin, in addition, may be quite dry and scaly and often shows brown pigmentation in the folds of the body.

The patient usually shows a fairly marked cervicothoracic kyphosis which accounts for the loss of height of which he may complain. The Roentgen-ray examination of the spine in these cases shows a marked porosity of the bone due to the loss of calcium and a wedging of the bodies of the vertebrae in the kyphotic region. X-ray examination of the other bones also frequently reveals porosity. The skull, too, is usually involved, and the sella turcica, while seldom enlarged, shows thinning of the clinoid processes, floor and dorsum sellae, not often as a result of local pressure, but as a part of the general process.

The blood pressure, both systolic and diastolic, is almost invariably high and the fundi oculi frequently reflect this state in the form of retinal hemorrhages, exudate, tortuosity and sclerosis of the blood vessels.

Occasionally there is a distinct, though not very marked, polycythemia with a red blood cell count of five and one-half to six and one-half million. In about a third of the patients, hyperglycemia and glycosuria are present.

The basal metabolic rate has been measured in a few of the cases reported and was found to vary between  $-33$  and  $+33$ , although the tendency is for it to be somewhat above the normal.

*Complications* The influence of the abnormal secretions of the basophilic adenoma may result in numerous complications associated with hypertension (e.g., cerebral hemorrhage, chronic nephritis, retinal hemorrhages), with decalcified bones (e.g., spontaneous fractures, kyphosis), with glycosuria (e.g., a tendency to acquire infections, even diabetic coma).

*Diagnosis* The striking clinical picture makes the diagnosis of the syndrome extremely easy. The only difficulty is that known cases of

apparently the same disease have been found which were believed due to tumors arising from the adrenal glands, and in whom no tumor of the pituitary gland was said to exist Since it is known that the pituitary adenomas are often very small, the failure to find them in the past is not completely acceptable evidence of their absence In relation to this condition, the student is witnessing a chapter of medical history in the making Harvey Cushing has built up his evidence like a true veteran with full awareness of all the pitfalls that await the explorer in a new field For lack of material, however, some of the facts still need confirmation

*Prognosis* Pituitary basophilism is a chronic disease, the average patient presents himself for hospital study more than seven years after the onset of the first symptom Dr Cushing followed his first case for over twenty years after he first saw her Death usually results from some intercurrent disease, or one of the complications mentioned above The disease has been known to become arrested spontaneously Some hope exists that improvement may be brought about by treatment of the primary tumor of the pituitary gland either directly by surgery or indirectly by the Roentgen ray

*Treatment* Following the analogy of the other adenomas of the hypophysis, the treatment which immediately suggests itself is either extirpation of the tumor by surgical means, or its devitalization by roentgenotherapy, or both So far, I know of no case that has been successfully operated upon Several patients, however, have shown remarkable improvement following radiation directed to the region of the pituitary body

### HYPOPITUITARISM

*Definition* Hypopituitarism is a condition resulting from interference with secretion of the pituitary body either by tumor, degeneration or infection of the gland The effects vary with the degree of functional disturbance of the pituitary and its neural connections with the hypothalamic portion of the brain, as well as with the age of the patient at the time of onset of the disease

*History* The association of pituitary tumor with blindness has been recognized since 1705 when Vieussens<sup>17</sup> reported the case of "le cardinal de Bonsy" who showed at necropsy a pituitary tumor the size of a hen's egg From that time a relatively large number of cases were reported,

showing disturbance of vision with such tumors. The first known case in which obesity was linked with the combination of pituitary tumor and visual disturbances was reported by Mohr<sup>18</sup> in 1840. It was not, however, until after acromegaly was described in 1886 and the symptoms of this disease linked with a tumor of the pituitary gland that the constitutional changes in patients harboring a pituitary tumor were carefully scrutinized. The demonstration of pituitary tumors in the absence of acromegaly was considered proof against the assumption that the acromegalic symptoms were a result of the tumor. The recognition that there was a difference in the character of tumors primarily originating in the pituitary gland did not come until 1900 when Benda<sup>5</sup> produced incontrovertible microscopic proof of this contention. In 1901, Froehlich<sup>19</sup> described the case of a 14-year-old boy with headache, vomiting and obesity, underdeveloped genitalia and absent pubic and axillary hair, who harbored a tumor in the region of the pituitary gland. To this syndrome, Bartels<sup>20</sup> later gave the name of "dystrophia adiposogenitalis." This was considered a prototype of hypopituitarism until Philip Smith<sup>21</sup> showed by his experiments with rats that, in all likelihood, the so-called pituitary obesity was probably not a result of direct disturbance of the pituitary gland but rather of the neighboring hypothalamic portion of the brain. By his experiments, the distinction between a lesion of the neighboring brain and of the pituitary body was first made. Previous experiments were inconclusive since, as a rule, in an attempt to produce the one lesion, the other was also inadvertently made. In the experiments which he carried out to show the effect of ablation of the anterior lobe of the pituitary gland without injury to the brain, he was able to demonstrate that in immature individuals growth ceases, sexual development fails to take place, but obesity does not occur. In adults who have attained their full growth, very little effect is noted aside from dystrophy of the gonads and a thinning and falling out of the hair.

#### CHROMOPHOBE PITUITARY ADENOMA

The commonest cause for hypopituitarism is the chromophobe adenomatous tumor of the anterior lobe of the pituitary gland, which has no known secretion of its own, and which compresses and interferes with the function of the normal pituitary body.

*Etiology* These tumors are by far the commonest variety affecting the pituitary gland, making up about two-thirds of all the adenoma cases

It is a disease of adult life, being fairly evenly distributed in the third, fourth and fifth decades at the time when the patients seek aid in a hospital

*Morbid anatomy* This tumor is usually soft, brownish red in appearance, with a fibrous capsule of varying thickness. It is composed of very thick columns of cells separated by septa of connective tissue carrying delicate capillaries. The cells are elongated, columnar, and often stand at right angles to the connective tissue septa. They have rather indistinct boundaries and their pale staining cytoplasm contains no granules other than mitochondria. The nuclei are small, oval with heavy chromatin material.

The other members of the endocrine series, especially the thyroid, adrenals and gonads, as well as the other organs of the body, are likely to be smaller than normal, in contrast to the condition seen in acromegaly.

*Symptoms* The chromophobe adenomas are again large tumors and produce, as a result of local pressure, headache, primary optic atrophy, bitemporal hemianopia, and roentgenographic evidence of enlargement, atrophy, often indeed, complete destruction of the sella turcica. If the growth continues to expand, pressure upon the oculomotor, trochlear and abducens nerves may result in strabismus, ptosis and pupillary changes. At times, the olfactory tracts may be compressed with resulting unilateral or bilateral anosmia.<sup>22</sup> Extension of the tumor outside of the confines of the enlarged sella turcica may result in pressure upon the hypothalamus causing at times polyuria and polydipsia (diabetes insipidus), or if it extends laterally and compresses the uncinate region, may cause hallucinations of smell. In rare instances, these tumors grow so large that they extend up far enough to obstruct the foramen of Monro, which prevents egress of fluid from the lateral ventricles, thus producing an obstructive hydrocephalus with all the signs of increased intracranial pressure.

Just as constant as the local pressure signs above described, are the constitutional changes accompanying this tumor. Usually the first of these symptoms to appear and the most constant is amenorrhea, or, in the male, loss of sexual libido and eventually also of potency. Next in frequency are atrophic changes of the skin, thinness and dryness of the hair on the head, loss of body hair, scantiness of axillary and pubic hair, the latter even in males, being feminine in distribution. About 80 per cent

of the patients show an abnormal degree of obesity which is characterized by a fluctuation in body weight, so that a gain or loss of 10 to 15 kilograms in a year is not unusual. The basal metabolic rate in these patients is usually low, the average being around 20 per cent below normal. This may be responsible for the sluggishness of these patients, their slow pulse and occasionally subnormal temperature. Since the disease has its onset, as a rule, after adolescence, infantilism is seldom seen accompanying it, although the size of the male genitalia is frequently within the lower ranges of normal.

*Diagnosis* Since tumors causing hyperpituitarism are easily diagnosed by the constitutional changes they produce, the differentiation of chromophobe adenomas from them is relatively easy. Difficulties may arise, however, in distinguishing the chromophobe adenoma from other tumors in the region of the sella turcica, such as craniopharyngioma (bucconeural tumor), suprasellar meningioma, glioma of the optic chiasm, aneurysm of the circle of Willis, chordoma, angioma, cholesteatoma, tuberculoma or gumma. Some of these conditions resemble clinically the chromophobe adenoma by producing similar focal symptoms, others reproduce the endocrinological changes, while some produce both. Differentiation, however, can usually be made by considering the history, Roentgen-ray and encephalographic data.

*Prognosis* Chromophobe adenoma of the pituitary gland is a more rapidly progressive disease than the eosinophilic tumor of acromegaly. It seldom lasts over ten or fifteen years, and frequently, even in spite of treatment, leads to blindness, headache, paralyses resulting from intracranial extension of the tumor. Anemia, asthenia and intercurrent infection frequently are seen in the terminal stages of the disease.

*Treatment* Treatment is again either surgical, roentgenological, or both. The results of neither, nor both in combination, are as good as in acromegaly. The techniques employed are about the same as in acromegaly.

#### SIMMONDS' DISEASE<sup>23</sup>

A very extensive, at times even complete, degeneration of the pituitary gland sometimes occurs. This may come about as a result of trauma, infarction or infection of the gland. It produces a rapidly fatal, progressive disorder described as hypophysial cachexia. The patient becomes rapidly emaciated and extremely weak. He seems to age very quickly and usually dies of some intercurrent infection. Recent reports

in the literature of improvement in examples of this disease, as a result of parenteral administration of anterior pituitary hormones, have appeared. Reliably potent preparations of these hormones are not yet available commercially and this treatment is still experimental.

In the diagnosis of this disease special care should be taken to differentiate it from anorexia nervosa which Sir William Gull described 70 years ago. This superficially presents a similar picture but is actually a functional disease based upon psychological maladjustment and is amenable to psychotherapy.

### DWARFISM

Aside from the failure of development in stature resulting from congenital abnormalities like achondroplasia, states of malnutrition and insufficient vitamins, many of the pathologically small statures are probably related to dysfunction of the pituitary gland. In some of these conditions, gross abnormality of this gland can be demonstrated. In others, this does not always seem to be the case.

*Hypophysial infantilism* One form of dwarfism in which a lesion of the pituitary is usually demonstrable is known as the Levi-Lorain type. This condition is often the result of infarction of the glandular portion of the pituitary, occurring during some acute infectious disease of childhood with a resulting disturbance probably of both the growth and sex factors of the pituitary hormone. The patients usually tend to retain their childlike proportions. Their bones are of light construction, the skin is delicate, the primary sex organs never develop beyond the state of childhood, and secondary sex characteristics do not make their appearance. These patients are usually normal intellectually, indeed, are sometimes exceptionally bright. They maintain fairly normal health and make up a fairly large proportion of the dwarf colony in circuses. They seem, however, to have relatively poor resistance to infection and usually die relatively young of some infectious disease. Occasionally this type of dwarfism is accompanied by mental deficiency.

*Primordial dwarf* In contrast to the childlike proportions of the Levi-Lorain dwarf, the primordial dwarf, whose stature is frequently below that of the former, nevertheless, develops the proportions of an adult. These individuals appear as miniature men and women, their sexual function is normal, ossification of the skeleton takes place at the normal age. The condition is hereditary and is transmitted through the

father The famous general, Tom Thumb, and his family were examples of this condition The pituitary gland, although small, so far as is known shows no gross abnormalities

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## HYPERTENSION—THE PROBLEM, THE STUDY, THE FUTURE\*

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**T**HE aeroplane glides through the sky billowed up by the pressure of air beneath its wings. The streamlined locomotive rushes across the continent powered by Diesel engines. This engine turns because heat is generated by compression of the gases, thus causing combustion of the fuel. An electric motor spins due to the reaction of the magnetic fields created around the coils of wire in its revolving parts. Hypertension is caused by a spasm of the smaller blood vessels throughout the body.

Each of these above statements are facts. Merely repeating them, without further elaboration, does not necessarily show a very profound understanding of the details or the ground work of knowledge necessary to evolve them. When a breakdown comes, one needs more working knowledge than general facts to remedy the difficulty. In the case of hypertension, have we not been concerned with the end-result, "the tension," found in the blood vascular system of the patient said to have high blood pressure? Our attention being focused on this fact, it is agreed that the arterial spasm must be relieved to prevent disaster. Treatment by medication has been the method at hand. It has long been directed in a pseudo-magic attempt to lower that tension. The clinician had little time except to try the various drugs on his willing patients. This method of "pouring oil" on the "troubled waters" is not the mechanic's method of attacking his problem. He seeks out the faulty part of the motor and treats it. He knows the result or dysfunction of the engine is due to a worn or broken part. The satisfactory performance will come when the defect is remedied.

### THE PROBLEM

In studying the basic facts of hypertension, the mechanic's procedure has been used, but the answer has been slow in evolving. It began a

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century ago, when Bright<sup>1</sup> called attention to the kidney in a patient dying with hypertension. This finding became so common that the kidney was agreed upon as the cause and the disease affecting it bore Bright's name. Gull and Sutton later noted that the disease was not confined to the kidney but all the smaller vessels throughout the body were involved. It followed from this observation that hypertension was regarded as a generalized vascular disease with the kidney only a small part of the process. No matter what view one takes as to the cat and the tail of this controversy, the real problem in understanding hypertension has to do with the character of the agent raising the arterial pressure. Not until we fully understand this, can any question be settled finally or satisfactorily. It is agreed there is more or less uniform narrowing of the small arteries and arterioles. There are three ways in which this narrowing might occur, namely, from a morphologic change in the vessels themselves, from a vasoconstriction of nervous origin, or from a stimulation of the vessel walls by chemical elements in the circulating blood.

It is generally accepted from the histologist's point of view, that the arterial narrowing morphologically is a fatty hyalin thickening of the intima and a hypertrophy of the media.<sup>2</sup> General agreement has it that the intimal change *per se* is insufficiently widely distributed to cause a rise of tension. On the other hand, the tendency for the peripheral arteries to show marked changes secondary to heat and cold stimulation leads us to believe that this thickening is a work hypertrophy similar to that observed in cardiac musculature.<sup>3 4 5 6 7</sup>

Those sponsoring the nervous hypothesis do not clearly state the way overactivity of the vasoconstrictor nerves is brought about. They rely mainly on the evidence derived from the "cold pressor test" and from the effects noted in dividing the sympathetic supply to the abdominal viscera. On the other hand, Pickering and Kissin<sup>8</sup> have shown that the cold pressor test with a marked response to cold is not peculiar to essential hypertension. It is found in many normal individuals. So that this test cannot be considered as the last word in drawing the conclusion that there is an overactivity of the nervous mechanism to the arterioles. The operations for denervating the splanchnic area are of two kinds: section of the anterior spinal roots from about the sixth thoracic to the second lumbar, and section of the major and minor splanchnic nerves above or below the diaphragm with removal of the adjacent sympathetic ganglia. These two operations seem to produce similar effects on

arterial blood pressure in essential hypertension <sup>9,10,11</sup> In some patients the fall of blood pressure is profound and persistent In most cases a considerable fall is ultimately followed by a return to approximately the preoperative level, and in a few the blood pressure is unaltered

### THE STUDY (EXPERIMENTAL)

The study concerns the last possibility, that of a chemical substance present in the blood What work has been done regarding this? Where does it lead us? What are the inferences from the results? Animal experiments show that arterial tension is increased by procedures that decrease the blood flow through the kidney These procedures have been varied in method but the results are the same They are

- 1) Excision of varying amounts of renal tissue
- 2) Constriction of the renal veins <sup>12,13</sup>
- 3) Production of an interstitial fibrosis of the kidney by exposure to x-rays <sup>14</sup>
- 4) Ligation of one or both ureters <sup>15,16,17</sup>
- 5) Partial ligation of the renal arteries <sup>16,17,18,19</sup>
- 6) Compression of the renal arteries with adjustable clamps <sup>20,21,22</sup>

Most significant and instructive seems to be the compression method of Goldblatt and others in which renal ischemia is produced by adjustable silver clamps On the other hand constriction of equally important blood vessels, as the superior mesenteric artery, does not cause elevation of blood pressure Therefore, we are led to believe it is not constriction of the blood supply to any organ that gives this result, but a specific organ, the kidney However this work was open to criticism It required further proof to convince investigators that the application of clamps to the arteries did not cause reflex spasm This type of hypertension was not prevented or relieved by

- 1) Denervation of the kidney pedicle <sup>23,24,25</sup>
- 2) Excision of the splanchnic nerves <sup>26</sup>
- 3) Complete sympathectomy <sup>27</sup>
- 4) Complete destruction of the spinal cord <sup>24,28,29,30</sup>

Therefore a chemical substance was presumed to come from the ischemic kidney, acting on the blood vessels themselves or through the vasoconstrictor nerve-ends This is borne out partially by the following

- 1) A "pressor" substance can be found in extracts of normal kidneys <sup>31</sup>

- 2) Much more of this "pressor" substance is found in extracts from diseased kidneys<sup>32</sup>
- 3) Excision of the experimental ischemic kidney at the height of the hypertension it produces, allows a prompt return of the blood pressure to normal<sup>21,33</sup>
- 4) Transplantation of the ischemic kidney from the loin of one dog to the groin or neck of another produces the same result in the second experimental animal<sup>34,35,36</sup>

**TABLE I**  
**INTERFERENCE WITH RENAL CIRCULATION**  
*This is accomplished clinically by*

**I Intrinsic, infection within the kidney—**

Bilateral resulting from	Benign prostatic obstruction Partial occlusion of ureters Accompanying bladder Bilateral infection	stone diverticula malignancies	causing clinical pyelonephritis
Unilateral resulting from	Pyelonephritis Calculi Contracted kidney Tuberculosis of kidney	from infection from trauma	

**II Extrinsic, effecting interference on the renal artery circulation**

Unilateral	Malposition of the kidney Abnormal course and position of artery Hydronephrosis with pressure on artery Atheromatous plaques Infarct of kidney Thrombosis with recanalization

## EXAMPLES

## I Intrinsic infection within the kidney

## BILATERAL

- 1 Cohnheim<sup>3</sup> as far back as 1877 reported cardiac hypertrophy presumably from hypertension with urinary obstruction and a large stone in the bladder
- 2 Passler,<sup>33</sup> 1906, reports a case of anuria of 12 days duration due to a carcinoma of the cervix partially obstructing both ureters, accompanied by hypertension
- 3 Longcope and McClintock<sup>34</sup> in 1910 called attention to the clinical relationship of chronic pyelonephritis and hypertension
- 4 Biasch<sup>35</sup> in 1911 reported three cases of genital carcinoma with urinary obstruction and elevated blood pressure readings
- 5 von Monakow and Mayer<sup>36</sup> in 1918 reported cases of prostatic hypertrophy with reduction of elevated pressures following bladder drainage
- 6 O'Connor,<sup>37</sup> 1920, and again in 1923 noted a fall of blood pressure in seventy-four cases of bladder neck obstruction following satisfactory bladder drainage
- 7 Staemmler,<sup>38</sup> in 1932, collected thirty cases of pyelonephritis with contracted kidneys and marked elevation of blood pressure and cardiac hypertrophy
- 8 Fishberg<sup>39</sup> in 1934 commented on several cases of hypertension associated with urologic disease
- 9 Ritch,<sup>40</sup> 1936, reported the benefits of urologic treatments in six cases of hypertension
- 10 Longcope<sup>41</sup> more recently reported hypertension in 50 per cent of his twenty-two cases of chronic pyelonephritis
- 11 Butler<sup>42</sup> showed a similar relationship in children of hypertension and pyelonephritis in fifteen of his cases
- 12 Weiss and Parker,<sup>43</sup> 1938, in 100 cases of pyelonephritis showed a relationship between the degree of infection and the magnitude of the hypertension. They estimate 15 to 20 per cent of cases of malignant hypertension are due to pyelonephritis

UNILATERAL INFECTION—removed surgically followed by changes in blood pressure comparable to the result reported in experimental animals

- 1 Butler<sup>44</sup> reports two children with hypertension having unilateral pyelonephritis cured by nephrectomy
- 2 Leidbetter<sup>45</sup> mentions two cases of unilateral tuberculosis with readings of 160/100 to 180/100. In one of these the pressure has returned to normal since operation
- 3 Barker and Walters<sup>46</sup> review a case with immediate return of blood pressure to normal after removal of an infected kidney, the site of a stone, 13 years previously
- 4 Author's case had a kidney stone known to be present 16 years. With nephrectomy a definite fall of blood pressure was noted. Although this did not return to a normal level, disappearance of headaches and improvement in hearing followed removal of the poorly functioning kidney (Published elsewhere)
- 5 Longcope,<sup>47</sup> reporting a case with a stone impacted in one of the calices and accompanied by pyelonephritis and hypertension, makes note of the fact that with infection, hypertension comes long before there is any evidence of renal insufficiency

**II Extrinsic, effecting interference with the renal artery circulation****MALPOSITION IS WELL EXEMPLIFIED IN THE CASE OF**

- 1 Leadbetter and Burkland<sup>4</sup> report an ectopic kidney located in the pelvis causing constriction and stretching of the renal vessels with subsequent hypertension Nephrectomy resulted in a cure

**HYDRONEPHROSIS HAS BEEN SEEN NOT INFREQUENTLY WITH BLOOD PRESSURE CHANGES**

- 1 Lohlein,<sup>5</sup> 1917, reviewed two cases of hydronephrosis with blood pressure readings as high as 210/140
- 2 Morton<sup>6</sup> had a definite fall of the blood pressure to normal, in his patient following nephrectomy for a hydronephrotic kidney with an anomalous vessel
- 3 Nesbit<sup>7</sup> has reported several interesting cases in both this and the infectious group

**ARTERIOSCLEROTIC PLAQUES WITHIN THE RENAL BLOOD VESSELS DO NOT OFTEN INTERFERE WITH RENAL CIRCULATION**

- 1 Freeman and Hartley<sup>8</sup> observed a case in which a single kidney was made ischemic and hypertension resulted due to an atheromatous plaque at the entrance of renal artery

**THROMBOSIS OF THE RENAL ARTERY MAY ACCOUNT FOR MANY CASES, A FEW OF WHICH HAVE BEEN RECOGNIZED**

- 1 Boyd and Lewis<sup>9</sup> case showed a huge infarct in the kidney with marked hypertension Nephrectomy resulted in a return of blood pressure to 124/84
- 2 Welty<sup>10</sup> reviews a group of eleven cases dying with thrombosis of the renal artery all of which were hypertensive
- 3 The unilateral contracted kidney with hypertension seems a very likely end result where the condition has partially healed by recanalization of the vessel

**THE STUDY (CLINICAL)**

The value of experimental work depends on the way it can be applied clinically Is it not true, that our fastest aeroplanes are often designed by capable pilots? Having learned the theoretical mechanics of hypertension from the physiologists, the pilots or clinicians are stepping into the field with new designs or application for this knowledge They are fitting surgery and urological treatment to the relief of a certain group of these patients If removal of the ischemic kidney in the experimental animal allows blood pressure to return to normal, the same should result in the human In our kidneys no silver clamp has been applied, but infection has applied thousands of clamps to the smaller blood vessels Abnormal position and pathological conditions have likewise constricted the renal artery We may classify the clinical situations as outlined in Table I

## THE FUTURE

Large groups of cases with hypertension have been reviewed in an attempt to correlate the urinary tract findings and blood pressure readings. Schroeder and Steele<sup>57</sup> in 71 cases of essential hypertension demonstrated some abnormality in the intravenous urography in 50. Their reported data is as follows:

I Lesions suggesting obstruction to the flow of urine were found in 36 patients

- a) There was well marked bilateral hydronephrosis in 4
- b) Moderate hydronephrosis bilateral in 7
- c) Unilateral hydronephrosis present in 20
  - d) " " moderate in 11
  - e) " " mild in 9
- f) Hydronephrosis mild or moderate associated with disease of the other kidney as follows
  - 1 Marked inflammatory contraction and distortion of the renal pelvis
  - 2 Marked ptosis
  - 3 Total absence of function
  - 4 Replacement of the kidney by calcified cysts
- g) Hydroureter, five patients
- h) Double kidney with mild unilateral hydronephrosis

II Renal Calculi were seen in five patients

- a) In pelvis or calices
- b) Associated with hydronephrosis
- c) Combined with total absence of function of the opposite kidney

III Miscellaneous lesions were also noted

- a) Absence of evidence of function by excretion of dye for intravenous urography, four patients
- b) Two patients with ptosis of one kidney
- c) Bilateral duplication of kidneys and ureters
- d) Marked distortion of calices perhaps the result of old inflammation
- e) Persistent sharp angulation of the ureter

TABLE II

MAHER AND WOSICK<sup>5</sup> SUMMARIZE 101 CASES SHOWING THE FOLLOWING PRIMARY URINARY TRACT PATHOLOGY ALL ASSOCIATED WITH HYPERTENSION

Prostatic obstruction including complications of upper urinary tract	31
Chronic pyelonephritis with complications	27
Renal stone and complications	18
Prolapse of uterus with hydronephrosis and infection	7
Diverticula of bladder and complications	5
Urethral stricture (male)	4
Cancer of bladder with ureteral obstruction and infection	2
Renal tumors	2
Congenital cystic kidney	2
Bladder stone	1
Congenital absence of kidney	1
Vesicovaginal fistula	1

The experimental work and the clinical examples mentioned above are a distinct challenge to every enterprising and thinking man of medicine. It becomes a problem to see which patients fall into the group that can be cured by surgery or urologic treatment.

Urology has gone far as a specialty with the addition of the x-ray and the kidney function tests, but as yet these leave much to be desired and there is great need for an accurate method to evaluate carefully and easily the kidney function early in the disease. At the present time we have no explanation of the fact that some patients with pyelonephritis develop hypertension before renal insufficiency while some develop it only after renal damage has become marked and still others die of uremia with very little hypertension.

It is evident that hypertensive disease can be divided into at least two categories. One contains that group of cases in which there is local inflammatory, suppurative or obstructive impairment of one or both kidneys, causing hypertension. The second group contains those instances of so-called essential hypertension in which no local renal factor has as yet been demonstrated. Reduction of hypertension by nephrectomy has been accomplished in those cases where infection was the cause of lessened renal blood flow. Study of the blood vessels in the second

group shows a hypertonus of the efferent glomerular arterioles that tends to produce a degree of renal ischemia<sup>59</sup> Paunz<sup>60</sup> showed in the dog that a new blood supply to the kidney can be supplied by omentopexy, the vascularization thereby effected being adequate to maintain urine formation after ligation of the artery of the operated kidney and even after removal of the opposite kidney. This procedure suggests that we may have an approach to the problem of treatment of this type of case in the human. It is a problem that can only be approached cautiously after a thorough knowledge of filtration rate, renal blood flow and mass of tubular excretory tissue<sup>61</sup> It is an established fact that the formation of urine is by a combination of three processes. The first, a filtration process, takes place in the glomerulus. The second, the protein-free filtrate passes on down to the tubules where the water and valuable constituents as chloride and glucose are reabsorbed. A third process, which is perhaps the most important, is that of tubular excretion<sup>62</sup> So complete is this process that excretion of many substances result in almost completely removing them from the plasma before the blood reaches the renal veins. The tubular excretion removes about 94 per cent of phenol-sulphonphthalein, while only about 6 per cent is removed by glomerular filtration. The organic iodine preparations (diodrast, hippuran and iopax) have this same characteristic way of removal. So it is easy to see that it is possible to measure quantitatively the amount of intact tubular epithelium of the kidney by measuring the rate of excretion of the dye or chemical. Here two practical difficulties arise, in that these latter substances must be given by continuous intravenous infusion in order to maintain a constant plasma concentration, and the analysis of urinary secretion of diodrast and hippuran is at present a tedious and difficult matter. However, we hope that simpler methods of measuring the renal blood flow will be available in the future. It would seem that since tubular excretion carries 94 per cent of the load, glomerular filtration is relatively unimportant, so we need not be concerned with a substitute for normal vascularization in consideration of the value of omentopexy. It is the opinion of competent observers<sup>61</sup> that man can get along with a very small residue of glomerular function, providing the complicating features of renal destruction are eliminated. These complicating features might in a considerable measure be eliminated if the accessory blood supply afforded by omentopexy served only to increase the blood flow to the tubules. Crile<sup>63</sup> recently has suggested that renal decapsulation be

done as in adjunct to the operation of celiac ganglionectomy. He feels this procedure has contributed something in addition to the operation he has been championing. I feel no doubt this is due to the increase in renal blood flow by collateral circulation established at the convex surface of the kidney.

So for the future we have the offer of hope to the patient with an infection be it unilateral, of improvement in his hypertension. If bilateral infection is present urologic treatment with release of obstruction, removal of irritating growths and calculi may give the result desired. Every case of hypertension deserves the right to have thorough urologic investigation before the stamp of incurability is placed upon him. The idea of omentopexy is being studied. Perhaps in time satisfactory study and technique will develop this into a practical procedure. We and our forefathers have erred long in hunting for a magic drug that will reduce pressure. Physiologists and clinicians have brought into the light some facts for understanding this disease. May we in the future look on every case of hypertension with these facts in mind!

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## PROCEEDINGS OF ACADEMY MEETINGS

### SECTION MEETINGS

FEBRUARY 1—*The New York Academy of Medicine* Executive session Reading of the minutes "Papers of the evening"—a] Sympathin on allergy—a] Mechanism, Matthew Walzer, Attending in Allergy, Jewish Hospital of Brooklyn b] Clinical considerations, Robert A. Cooke, Assistant Professor of Clinical Medicine, Cornell University Medical College, c] Allergy in children Lewis Webb Hill, Associate in Pediatrics, Harvard Medical School, Discussion, Will Cook Sprin, Joseph Hartava "Report on election of members

FEBRUARY 15—*The Harvey Society in affiliation with The New York Academy of Medicine* The Fifth Harvey Lecture, "Physiology of the Renal Circulation, Homer W Smith, Professor of Physiology, New York University College of Medicine

### SECTION MEETINGS

FEBRUARY 2—*Section of Surgery* Reading of the minutes "Presentation of cases"—a] Periarteritis nodosa simulating surgical abdomen, Philip Allen, Discussion, Paul Klemperer, b] Successful suture of stab wound of heart, Joseph B. Stenbuck, Discussion, Samuel S. Palev (by invitation), c] Cases illustrating papers of the evening, Samuel

A. Thompson, Milton J. Rausbeck "Papers of the evening—a] The surgical treatment of coronary artery disease with special reference to cardiopericardiotomy, Samuel A. Thompson Discussion, Henry W. Cave, Frederic W. Bancroft, b] The selection and management of patients in the surgical treatment of coronary disease, Milton J. Rausbeck Discussion, Charles F. Tenney, Harold J. Stewart "General discussion "Executive session

FEBRUARY 6—*Section of Dermatology and Syphilology* Presentation of cases—a] Vanderbilt Chue, b] Miscellaneous cases "General Discussion "Executive session

FEBRUARY 8—*Section of Pediatrics* Reading of minutes "Papers of the evening"—a] Diabetes mellitus in one of identical twins—follow-up studies of both twins, Alfred F. Fischer, Discussion by H. Rawle Gevlin, b] Vitamin A status of children as determined by dark adaptation, Charles Haig (by invitation), Jacques M. Lewis, Discussion by Selig Hecht (by invitation), c] Cystic hygroma in infants with presentation of three case histories, Abraham Low d] A comparative study of therapeutic procedures in scarlet fever at the Kingston Avenue Hospital, Henry Rascov (by invitation) Sidney Nussbaum (by invitation) "General discussion "Executive session

**FEBRUARY 13—Section of Neurology and Psychiatry** Reading of minutes ¶ Papers of the evening—a] Report of two cases presenting rhythmic palatal myoclonus, J T Dobson (by invitation), Henry Alsop Riley, Discussion, Samuel Brock, b] Dietetic and related studies in multiple sclerosis patients, Richard W Brickner, Norman Q Brill (by invitation), with the assistance of Frances H Naylor, B Sc, MA and Kathryn Montgomery, B Sc, Discussion, Tracy J Putnam (by invitation), Israel S Wechsler, c] Hemangioblastoma of the cerebellum Clinical, surgical and roentgenological aspects, Leo M Davidoff, Cornelius G Dyke, Discussion, Henry Alsop Riley, Charles Division ¶ Executive session

**FEBRUARY 14—Special Meeting on Syphilis of the Section of Dermatology and Syphilology** Presentations — a] Unusual cases of skin, visceral and neurosyphilis, b] Complications arising from syphilis

**FEBRUARY 16—Section of Orthopedic Surgery** Reading of the minutes ¶ Presentation of cases—Chondral fracture of the patella, Joseph E Milgram (by invitation) ¶ Papers of the evening—a] Delayed reduction of fractures, John R Moore, Philadelphia (by invitation), Discussion, Mather Cleveland, b] Re-section of the elbow, B Franklin Buzby, Camden (by invitation), Discussion, Philip D Wilson, e] Injury to the femoral cartilage by the medial meniscus, Alan DeForest Smith, Byron B King (by invitation) ¶ General discussion ¶ Executive session

**FEBRUARY 19—Section of Ophthalmology** Instruction hour 7 00 to 8 00 Non-suppurative diseases of the cornea, part II, Ralph I Lloyd Demonstration of Slit Lamp Cases 8 00 to 8 30, Gordon M Bruce, Girolamo Boniceolto, Milton Berliner ¶ Reading of the minutes ¶ Presentation of cases—a] A self-setting cross cylinder, Joseph I Paseas, b] The intramarginal suture in lid re-

pair, Henry Minsky, c] Four cases of unusual traumatic stationary catareals, Daniel M Rolett (by invitation), d] Pseudotumor of the orbit, Willis Knighton ¶ Papers of the evening—a] Intravital color of the macula, Johan W Nordenson, Stockholm (by invitation), b] Harvey Cushing An ophthalmologist's appreciation, Bernard Samuels ¶ General discussion ¶ Executive session

**FEBRUARY 20—Section of Medicine** This meeting was held at the Einhorn Auditorium, Lenox Hill Hospital (131 East 76 Street) ¶ Reading of the minutes ¶ Presentation of cases treated by cryotherapy ¶ Papers of the evening, Symposium on cryotherapy (so-called artificial hibernation)—a] Rationale and description of method Conditions treated to date, carcinoma, leukemias, drug addictions Selection of cases rejections, acceptances John C A Gerster, b] Cardiovascular aspects, Charles E Kossmann (by invitation), c] Hematology (1) Carcinoma, (2) Blood dyscrasias, Carl Reich, d] Blood chemistry, Adolph Bernhard (by invitation), e] Bidal metabolism, Jacob Geiger (by invitation), f] Neurological aspects, Thomas K Davis, g] Temperature observations, Madge C L McGuinness, h] Urological observations, H R Kenyon, i] Pneumonias, John F Dixon (by invitation), j] Roentgenological observations, Frank Huber (by invitation), k] Biopsies and deaths (Rudolf M Piltz) (by invitation), l] Results to date pain control, clinical manifestations, local treatment (two cases), nursing details, P K Sauer (by invitation) Discussion opened by W Laurence Whittemore ¶ Inspection of cryotherapy room Guides were furnished to groups of 6 at 5 minute intervals, Victor Gang (by invitation)

**FEBRUARY 21—Section of Genito-Urinary Surgery** Reading of the minutes ¶ Presentation of cases—a] Interstitial cystitis with autopsy findings, Joseph Schwartz, A Hyman, b] Two unusual pyclograms with operative findings,

George A Fiedler (by invitation), c] Primary carcinoma of the ureter, M R Keen (by invitation), d] Hypernephroma in polycystic kidney with invasion of vena cava, R B Henline, e] Unusual bladder tumor of urachal origin, F C Hamm, f] Cortical tumor without symptoms, Martin J Loeb, g] Two cases of long surviving ureteral transplantation, A R Stevens, h] Foreign body surrounding penis with suggested new method of removal, D Makowski (by invitation), i] Embryomatosis of testis, M M Melicow (by invitation), j] Micro-acrophilic streptococcal infection of penis and urethra, Paul W Aschner, Frank L Melency "General discussion" Executive session

**January 21—Section of Otolaryngology**  
Reading of the minutes "Papers of the evening—from the Columbia-Presbyterian Medical Center Nasopharyngeal Tumors—a] Diagnosis (1) Pathological, Arthur P Stout (2) Otolaryngological, James W Babcock (3) Neurological, Samuel Brock, (4) Roentgenological, Cornelius G Duke b] Treatment, Roentgenological, Haig H Kasabach (by invitation) "Discussion, Kaufman Schliver, Randolph Kramer, Ross Golden, Israel S Wechsler, Maurice Leuz

**January 27—Section of Obstetrics and Gynecology** Reading of the minutes Program by the Morrisania City Hospital "Presentation of cases—a] Endometriosis treated with testosterone propionate, Leo Wilson, b] Pregnancy complicated by carcinoma of the cervix (3 cases), Milton J Goodfriend, c] Telangiectasia associated with central placenta previa, Frederick A Wurzbach, Jr "Papers of the evening—a] Observa-

tions on the use of stilboestrol, Abraham Abarbanel (by invitation) Discussion, Samuel R M Reynolds (by invitation), b] Critical analysis of cesarean section at the Morrisania City Hospital, Abraham B Tunis Discussion, Harvey B Mathews, Harry Arnow

#### AFFILIATED SOCIETIES

**January 17—Joint Meeting of New York Roentgen Society and Philadelphia Roentgen Ray Society** at Memorial Hospital, 44 East 68 Street Ralph E Herendeen, Chairman, Introductory remarks, C P Rhoads, Director of Memorial Hospital (Introduced by Dr James Ewing) "Papers of the evening—a] Some new problems in radiology, James Ewing, b] The relation of dosage in roentgens to size of portal, Hayes Martin, c] Diagnosis and treatment of cancer of the lung, Lloyd Criner d] Treatment of artificial menopause, Grace H Womble, e] Serum phosphotase studies as an aid in radiation therapy of bone tumors, Helen Q Woodward

**January 29—New York Pathological Society (in affiliation with The New York Academy of Medicine)** Case reports—a] Cirrhotic-Bauingarten cirrhosis of the liver, Amour F Iberi, Chester R Brown, b] Multiple hemangioendothelioma of lung, Alfred Plant "Papers of the evening—a] Correlation between clinical and experimental findings in cases showing invasion of the blood stream by staphylococci, Bernard Kleiger (by invitation), John F Blair (by invitation), b] Pathological changes of the nervous system in chronic alcoholism, Lewis D Stevenson (by invitation)

## IN MEMORIAM

## HANS HORST MEYER

The New York Academy of Medicine regrets to inform its fellowship of the death on October 8, 1939, of one of its most distinguished honorary fellows, Professor Hans Horst Meyer of Vienna. His association with the Academy began thirty-five years ago when his scientific contributions in pharmacology resulted in an invitation from the Harvey Society to deliver the first Harvey lecture in the Academy on October 7, 1905 on the Meyer-Overton theory of anesthesia.

Hans Horst Meyer was born at Insterburg (East Prussia) March 17, 1853, studied at the Universities of Koenigsberg, Leipzig and Berlin, graduated in medicine from the University of Koenigsberg in 1877, elected an Honorary Fellow of the Academy November 5, 1936. Introduced to the methods and literature of physiology by Mr. Jaffé at the University of Koenigsberg, he later became assistant in pharmacology to Oswald Schmiedeberg in Strasbourg.

In 1882, when 28 years of age, he was called to the professorship of pharmacology at the University of Dorpat (then Russia, now Estonia). In 1884 and for a period of twenty years thereafter, he occupied the chair in pharmacology at the University of Marburg, with such distinguished associates as the pathologist Ludwig Aschoff and the internist Friedrich Mueller. It was during this time that many of his fundamental contributions to pharmacology were made.

In 1904, he became professor of experimental pharmacology at the University of Vienna where he continued to serve until his retirement in 1924. In a period when the teaching of pharmacology was largely didactic, he first employed the experimental method of instruction.

In 1908, he refused a call to the professorship in Berlin, preferring to remain in

Vienna as head of the distinguished Institute for Experimental Pharmacology. There came numerous pupils from all parts of the world. Among his American pupils were Dr. George Whipple, now Professor of Pathology and Dean of the Medical School of the University of Rochester, Dr. Henry Gray Birbür, now Professor of Pharmacology at Yale University, and many other outstanding investigators. He is well known to most American physicians and students because of the comprehensive work, "Die Experimentelle Pharmakologie als Grundlage der Arzneibehandlung," which was published in collaboration with Professor Gottlieb of Heidelberg and later with his pupil and successor, Professor Ernst Peter Pick, who is now a resident of New York. An English translation of the eighth edition of this classic work was published in 1912. His latest work "Hypnotica" in collaboration with E. P. Pick, appears in "Handbuch der Normalen und Pathologischen Physiologie," vol. 17, Berlin 1926.

Aside from the many honors which came to him during the course of his long and fruitful career, such as the honorary fellowship in the Academy and in many other scientific societies, he was the recipient of honorary degrees from the Universities of Vienna, Koenigsberg, Marburg, St Andrews and Edinburgh. Professor Meyer's greatest achievement lies in having related pharmacology to biology and in establishing pharmacology as the basis of rational drug therapy. His influence upon experimental pharmacology will never be fully appreciated because of his scientific generosity and his modesty. The Institute of Experimental Pharmacology in Vienna had the most delightful atmosphere of mutual helpfulness and high endeavor. The lives of all who had the privilege of working under his guidance

were permanently affected by this spirit of scientific fellowship. He was beloved by all his students and associates in Vienna where he exerted a marked influence upon the entire faculty of medicine.

In characteristic fashion, retirement at the age of seventy failed to dim his scientific and professional ardor. For years thereafter, he continued to work in his institute, guiding the scientific work of the younger assistants. Like his great American colleague, William Henry Welch, the period of retirement from academic work in his chosen field served merely to open new vistas of useful activity. During the

World War and for some years thereafter he spent much of his time in the study of cardiovascular physiology and therapeutics at the famous Heart Station in Vienna where he had an opportunity in his later years to apply his knowledge of physiology and pharmacology more directly to the care of the sick.

The political turmoil of recent years and its destructive effect upon Viennese medicine saddened the last year of his life. Until the end, his true nobility of character and his interest and love for his associates and friends remained undaunted.

GEORGE BAEHR

#### DEATHS OF FELLOWS

MEYER, HANS HORST born at Insterburg (East Prussia), March 17, 1853, died in Vienna, October 8, 1939, studied at the Universities of Koenigsberg, Leipzig and Berlin, graduated in medicine from the University of Koenigsberg in 1877, elected an Honorary Fellow of the Academy November 5, 1936.

Introduced to the methods and literature of physiology by M. Jaffé at the University of Koenigsberg, he later went to O. Schmiedeberg at the University of Strassburg under whose direction he soon advanced to the position of assistant. In 1881 he qualified for a lectureship in pharmacology at the University of Strassburg. In the same year he was appointed professor at the University of Dorpat (then Russia, now Estonia). In 1884 he removed to Münsterburg where he taught for twenty years. During that period he accepted several invitations to give lectures in England and America. In 1904 he assumed the professorship of pharmacology at the University

of Vienna, which he retained until his retirement in 1924.

Dr. Meyer's greatest achievement lies in having established a close link between pharmacology and biology, and in having made pharmacology the basis of a rational medicinal therapy. His comprehensive work 'Die Experimentelle Pharmakologie als Grundlage der Arzneibehandlung,' Berlin and Vienna, 1910, published in collaboration with R. Gottheb (with an English translation of the 8th ed., 1932) is considered a classic. His latest work "Hypnotics" (in collaboration with E. P. Pick) appears in 'Handbuch der Normalen und Pathologischen Physiologie,' vol. 17, Berlin 1926.

VAN COTT, JOSIAH MARSHALL 160 Henry Street, Brooklyn, New York, born in New York City, June 12, 1861, died in Brooklyn, New York, February 8, 1940, graduated in medicine from the Long Island College Hospital in 1885, elected a Fellow of the Academy November 1, 1906.

Dr. Van Cott had practiced in Brooklyn for fifty-four years and was emeritus professor of pathology and clinical medicine at the Long Island College of Medicine, senior physician to the Brooklyn Hospital, consulting physician to the Kings County, St. John's, Methodist Episcopal and Willow Heights Hospitals, consulting pathologist

to the Brooklyn State and Long Island College Hospitals, president of the professional staff of the Brooklyn Hospital, and president of the Board of Trustees of the Hoagland Laboratories of the Long Island College of Medicine.

He was a Fellow of the American Medical Association, a Fellow of the American College of Physicians, a member of the New York Pathological Society, a member and former president of the Medical Society of the County of Kings (1909), and a member of the New York State Medical

Society and chairman of its Public Health and Education Committee 1912-1925 and its vice-president, 1927-1928.

WILNER, ANNA SAVONOVNA, 246 Beach 122 Street, Rockaway Park, Queens, New York, born in Smolana, Mogileff, Russia, August 26, 1874, died in Rockaway Park, Queens, February 10, 1940, graduated in medicine from the Woman's Medical College of the New York Infirmary in 1895, elected a Fellow of the Academy December 7, 1905.

BULLETIN OF  
THE NEW YORK ACADEMY  
OF MEDICINE



MAY 1940

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THE MEDICAL MANAGEMENT OF  
HYPERTHYROIDISM\*

HAROLD THOMAS HYMAN

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TERMINOLOGY

**T**HE term "hyperthyroidism" will be employed, for convenience, throughout this discussion to embrace all of the clinical states variously termed Graves' syndrome,<sup>1</sup> Basedow's disease,<sup>2</sup> exophthalmic goiter,<sup>3</sup> toxic adenoma,<sup>4</sup> and adenomatous goiter with hyperfunction.<sup>5</sup> The multiple terminology suggests the uncertain state of our knowledge. Historically, the captions lack accuracy, since the earliest satisfactory description was that of Caleb Parry<sup>6</sup> of Bath (1786). Clinically and physiologically, the implications of the nomenclature are even more disturbing. Exophthalmic goiter may be present without exophthalmos or goiter.<sup>7</sup> "Toxic adenoma"<sup>8</sup> implies a metabolic abnormality whose existence is doubtful. The term hyperthyroidism suggests, in the thyroid gland, an increased secretory activity which has never been demonstrated.<sup>9</sup>

DEFINITION

Clinical hyperthyroidism is commonly delineated by cataloguing the major symptoms of tachycardia, tremor, exophthalmos and goiter, to-

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gether with the minor manifestations which include nervousness, sweating, asthenia and diarrhea To these clinical manifestations, has been added the laboratory evidence of elevation of the basal metabolic rate The relationship of these diverse phenomena may be clarified by a consideration of the physiology of the thyroid, its related glands and the involuntary nervous system

### THE PHYSIOLOGY OF THE THYROID GLAND

The parenchymal cells of the thyroid gland abstract iodine<sup>10</sup> and tryptophan<sup>11</sup> from the circulating fluids and manufacture (a) a specific iodine-containing hormone, thyroxin<sup>12</sup> and (b) a colloid substance in which the iodine or thyroxin is stored in the thyroid lumina

Thyroxin probably leaves the gland through both lymphatics and veins Since the concentration of thyroxin in the blood of human patients cannot be directly measured, the demonstration of the hyperthyroid state is dependent upon presumptive evidence which is (a) histologic (b) pharmacologic (c) chemical

(a) Histologic inferences concerning the hyperthyroid state are based on the hyperplasia<sup>13</sup> of the gland that is commonly, but not invariably, observed Hyperplasia of the gland is not limited to hyperthyroidism It may occur in simple or endemic goiter<sup>14</sup> or human cretinism<sup>15</sup> The histological picture is independent of thyroid function but is dependent upon iodine storage,<sup>16</sup> a decreased concentration of the element giving rise to hyperplasia The tenet that hyperplasia indicates hypersecretion is not in accord with fact<sup>17</sup>

(b) Indirect pharmacological evidence of the presence of hyperthyroidism has been suggested through the resemblance of the clinical syndrome to the symptoms produced artificially by the ingestion of thyroid extract or the injection of crystalline thyroxin<sup>18</sup> Unfortunately, the pharmacologic resemblance to clinical hyperthyroidism is imperfect Carlson,<sup>19</sup> after extensive studies of thyroid feeding stated "It would require considerable imagination or an undue influence of one's wish or one's judgment to identify the symptom-complex of excessive thyroid feeding in experimental animals with exophthalmic goiter" Every clinician has known many patients who have taken thyroid extract over long periods of time in order to effect weight reduction These patients manifest transitory symptoms as the result of over-dosage with the drug The symptoms abate when the drug has been discontinued and disposed of

If true hyperthyroidism develops, it is a rare experience and more likely coincidental than of causal relationship. Exophthalmos is a prominent feature of clinical hyperthyroidism, yet it cannot be produced by thyroid feeding, it is frequently not ameliorated significantly by thyroidectomy<sup>20</sup> and may even progress in the face of an operative procedure sufficient to cause myxedema.<sup>21</sup> Poisoning with thyroid extract is not identical with clinical hyperthyroidism, though the two conditions have much in common.

(c) Indirect chemical inferences pertaining to hyperthyroidism have been suggested by studies of iodine metabolism. Low iodine figures in the blood are consistently found in endemic goiter.<sup>22</sup> In clinical hyperthyroidism, both high<sup>23</sup> and normal<sup>24</sup> quantities have been described—the latter particularly in patients whose disease has existed for more than a year. Failure to demonstrate a consistently increased blood iodine may not necessarily argue against the possibility of hyperthyroidism. It indicates merely that the ratio of manufacture to destruction or excretion of the hormone does not consistently lead to increased blood concentration. Curtis and Phillips<sup>25</sup> studied the entire iodine economy in patients with hyperthyroidism. They demonstrated a negative balance due to excessive loss of iodine in urine, blood, sweat and stool and suggested that there is a true "iodine diabetes" in hyperthyroidism. Even this important and interesting work leaves much to be desired of indirect evidence that hyperthyroidism exists. If hyperiodinemia suggests hyperthyroidism, what is the explanation of the relief of symptoms attendant upon iodine therapy? Surely, if increased blood iodine indicates hyperthyroidism, an added supply of the element should augment rather than ameliorate symptoms.

Though this hypothesis of hyperthyroidism is fascinating, the hyperthyroid state cannot be proven directly, by measurement, or indirectly by inferences from histologic, pharmacologic or chemical investigation.

The state of confusion concerning hyperthyroidism has been increased by theories concerning the toxicity of adenomata and the possible production of an altered thyroid secretion causing so-called "hyperdysthyroidism." The known facts concerning thyroid adenomata may be briefly summarized. Interpolated in the thyroid tissue, as in all other parenchymal tissue, there are frequently observed isolated and encapsulated rests or adenomata.<sup>5</sup> These function less actively than the non-tumor tissue of the surrounding gland.<sup>26</sup> They cannot of themselves in-

dependently hypersecrete or give rise to clinical symptomatology except to participate in a process initiated and perpetuated by the surrounding non-tumor tissue. There is no evidence of the secretion of an altered thyrovin molecule. Hypotheses suggesting toxicity of adenomata and the existence of hyperdysthyroidism<sup>27</sup> not only lack positive proof but there is much tangible evidence to refute their accuracy.

Though laboratory evidence is lacking for proof of the hyperthyroid state, it is a clinical fact that subtotal thyroidectomy<sup>28,29</sup> relieves most of the distressing symptoms of patients suffering from clinical hyperthyroidism. There is much to suggest that the role of the thyroid may be intermediary. The amelioration of symptoms following thyroidectomy may be due not only to a decrease in the production capacity of the thyroid gland but to the severance of a link in a chain of disturbed physiological mechanisms. If the role of the thyroid gland be of secondary importance in clinical hyperthyroidism, the aim of specific therapeutic procedure would be directed toward the correction of the more fundamental disturbance. In consequence, the possible participation of factors other than the thyroid gland warrants scrutiny. These factors may be sought (a) in internal secretory glands other than the thyroid, (b) in the involuntary nervous system, (c) in a psychosomatic mechanism of basic biologic significance.

(a) There are many clinical observations that suggest, in hyperthyroidism, a primary disturbance of internal secretory glands, other than the thyroid, with secondary thyroid participation.

1) Halsted<sup>30</sup> was so impressed with the thymic enlargement in hyperthyroidism, that he advocated and performed thymectomy.

2) Clinically, there are many interesting inter-relationships between thyroid and ovary. Women greatly outnumber men in the incidence of hyperthyroidism. Since amenorrhea is a frequent symptom of the disturbance, the various ovarian extracts have been employed<sup>31</sup>—all unsuccessfully.

3) An inter-relationship of thyroid and adrenal medulla was suggested by the work of Cannon and his collaborators<sup>32,33</sup>. Attempts were made to prove the existence of an increased output of epinephrin or a "sensitization" of the involuntary nervous system to the action of the epinephrin through synergism with thyrovin. These experiments, though they could not be confirmed, induced Crile<sup>34</sup> to approach the surgical therapy of clinical hyperthyroidism by denervation of the adrenal

medulla or partial removal of its substance, a practice not generally accepted and now abandoned

4) Marine<sup>35</sup> demonstrated an inter-relationship between adrenal cortex and thyroid. Destruction or freezing of cortex led to elevation of the basal metabolic rate and simulation, in laboratory animals, of clinical hyperthyroidism. Extracts of adrenal cortex are being tried therapeutically, but to no great avail, thus far<sup>36</sup>

5) More recently, Collip and others<sup>37</sup> isolated a thyrotropic substance in the anterior pituitary gland. Occasionally, a suggestion of the clinical inter-relationship is seen in the association of pituitary syndromes and hyperthyroidism. The thyrotropic hormone may produce, in laboratory animals, a syndrome simulating clinical hyperthyroidism. It does not seem reasonable to assume, however, that this is, in truth, the sole operating mechanism. The sella turcica has been irradiated<sup>38</sup> in the attempt to treat hyperthyroidism by reduction or inhibition of the thyrotropic hormone. This has yielded no clinical success. Because of the presumptive inhibition of the gonadotropic factor of the pituitary gland by the male sex hormone, testosterone has been employed<sup>39</sup> in an attempt to inhibit the thyrotropic factor as well. The results thus far have not been encouraging.

The present status of the inter-relationship of thyroid and other internal secretory glands may be summarized briefly. Many important interplays are demonstrable. These relationships are interesting and suggestive but therapeutically unfruitful. However, these physiological approaches to the elucidation of the mechanism of hyperthyroidism indicate a mechanism beyond the thyroid gland and suggest that, one day, our present forms of therapy may be "rendered archaic by the discovery, for the control of the disturbance, of some specific physiological or pharmacological agent"<sup>40</sup>

(b) The failure of the clinical physiologist to unravel the riddle of hyperthyroidism, through humoral mechanisms and glandular interplay, has led to many ingenious experiments bearing on a neurogenic mechanism via the involuntary nervous system. The presenting symptoms in clinical hyperthyroidism are sympathonimetic<sup>41</sup>—this term indicating that they may be produced by emotional or chemical stimulation of the thoraco-lumbar portion of the involuntary nervous system. Whatever may be the ultimate agency producing hyperthyroidism there is no doubt but that eventually the causative mechanism operates through the

intervention of the involuntary nervous system. Hence, it may be profitable to review the pertinent facts relative to these neurogenic structures.

The involuntary nervous system, sometimes called the autonomic or sympathetic nervous system, operates at a level below the threshold of consciousness, probably through centers located in the midbrain. Peripherally, it is subdivided into two mutually antagonistic divisions. The cranio-sacral or vagus system, with its characteristic pharmacodynamic responses to atropine and the acetylcholin group of drugs, need not occupy our attention. The vagal antagonist, the thoraco-lumbar or sympathetic system is certainly involved in the pathogenesis of hyperthyroidism. This system is stimulated by drugs such as adrenalin, producing sympathomimetic manifestations identical with the symptoms of hyperthyroidism.

We are ignorant of the factors that control the tonicity of the involuntary nervous system. With the exception of epinephrin, the principles derived from the ductless glands are not sympathomimetic. Were a state of hyperepinephrinemia demonstrable, the problem of hyperthyroidism might be considerably simplified but this state does not and cannot exist as shown by the assays, performed by Stewart and Rogoff,<sup>42</sup> of the blood of the inferior vena cava pocket. The fascinating and suggestive hypothesis of "emergency" hyperepinephrinemia<sup>43</sup> fails of physiological proof.

Studies of the electrolytes of the blood do not clarify the situation. The experiments of Soffer and his associates,<sup>44</sup> demonstrating specific diminution of organically bound magnesium in hyperthyroidism, may have important significance that is not evident today.

If physiologic and pharmacologic methods have failed to elucidate the role of the involuntary nervous system in hyperthyroidism, many clinical observations are suggestive. Virtually all patients who develop hyperthyroidism give a history of a preexistent instability of the involuntary nervous system, a clinical state for which Kessel and Hyman<sup>45</sup> suggested the name "Autonomic Imbalance". Autonomic imbalance is usually the precursor or diathesis on which hyperthyroidism is superimposed, when a metabolic disturbance, characterized by increased catabolism, supervenes. When the metabolic state is restored to normalcy the patient reverts to autonomic imbalance and the residual symptoms following the relief of hyperthyroidism are identical with the early symptoms of the constitutional autonomic imbalance.

(c) Patients with autonomic imbalance present psychic and emotional instability and a bewildering variety of functional disturbances in organs whose parenchymae show no evidence of organic change. The catalogue of symptoms and signs in autonomic imbalance include vasomotor instability, manifested by cold hands and feet with or without excessive sweating, flushing, blushing, blanching, urticaria and other neurodermatitides, lability of the pulse rate and blood pressure, disturbances in motility and tonicity of smooth muscle, and secretory alterations in glandular structures. Though the manifestations of autonomic imbalance may be legion, each patient presents an individual "reaction picture" evoked by emotion, fatigue or the introduction of specific drugs. There is no significant elevation of the basal metabolic rate. The thyroid gland may be normal. There are no positive laboratory findings that are pertinent to the symptomatology. There may be present the alterations in the adrenalin sensitivity and the creatin metabolism believed respectively by Goetsch<sup>46</sup> and Shorr<sup>47</sup> to be specific for hyperthyroidism.

The concept of autonomic imbalance is essential to the understanding of the problem of hyperthyroidism. Inherent in the discussion of the mechanism of hyperthyroidism is the consideration of the factors that regulate the tonicity of the involuntary nervous system. The knowledge of either one of these problems will go far to the solution of the other. Since thyroxin is not sympathomimetic and there is no proof that sympathomimetic activity can give rise, directly or indirectly, to significant augmentation of thyroxin effect, we are compelled to admit our ignorance of the mechanism by which these agencies participate in the production of hyperthyroidism.

If the mechanism of hyperthyroidism cannot be fully explained by humoral or neurogenic factors, it may not be amiss to inquire into broader biological implications.

Biologically speaking, thyroxin is not essential to life. Phylogenetically, the gland is first observed in amphibians where its function is characterized by (1) accelerating metamorphosis, in species that normally undergo this change or (2) actually producing metamorphosis in certain salamanders which, in nature, undergo no metamorphosis. These changes have led Uhlenhuth<sup>48</sup> to state "They demonstrate at what a phylogenetic stage the amphibians and perhaps the entire higher vertebrates would be if they had not developed the thyroid mechanism." In the higher vertebrates the main and, perhaps, the sole function of thy-

rovian is as a catabolist accelerating most, if not all, biologic and metabolic processes. Whether or not thyrovian contributes new functions is an academic point which need not concern us at this time. The phylogenetic appearance of the thyroid gland at the amphibian level and its catalytic function in the human economy are of profound significance in discussions of the etiology and pathogenesis of hyperthyroidism. To the best of our knowledge, hyperthyroidism occurs spontaneously only in man, and perhaps only in civilized man. McCarrison,<sup>40</sup> for example, never observed hyperthyroidism in the native Indian until Indian troops were sent to the First World War.

There is presumptive evidence that hyperthyroidism may be a disturbance of historically recent origin and that its incidence is rapidly increasing. The clinical appearance of the patient with hyperthyroidism is dramatic, easily recognizable and unforgettable. Though endemic goiter was known to the Egyptian and Grecian physicians and the painters of primitives, the first medical description of hyperthyroidism appeared in 1802. The four pioneers who described cases between 1802 and 1840, Flajani in Italy, Parry who practiced in Bath from 1780 to 1816, Graves of Dublin and von Basedow of Merseburg, reported a total of but fifteen patients. Certainly a practitioner today, comparable to Parry practicing in Bath for thirty-six years, sees more than five cases of hyperthyroidism. Could Parry, once recognizing hyperthyroidism, have missed other cases that occurred in his practice or was the disease so rare that he saw on the average but one case every seven years? The speculation is not idle, for if hyperthyroidism is a condition of recent origin and vastly increased incidence occurring only or almost exclusively in civilized man, the psychic component in its etiology and pathogenesis assumes greater importance. The explanation of our inability to observe or produce the syndrome in its entirety in experimental animals or to comprehend its mechanism in the clinic may rest on these biological and psychological grounds.

#### Etiology and Pathogenesis

From what has been said, it is apparent that we are today ignorant of the etiology and pathogenesis of hyperthyroidism. Not so long ago it was considered heresy to doubt that clinical hyperthyroidism was other than a syndrome produced by an increased output of the thyroid hormone. Today, all serious students of hyperthyroidism entertain con-

siderable doubt concerning the mechanism of this fascinating and baffling condition Means<sup>21</sup> in his recent and excellent treatise on the thyroid gland and its disorders writes "Since, in the majority of cases of exophthalmic goiter, no etiologic agent or likely causative factor thus far has been found and since the disease has not been perfectly reproduced in experimental animals, it must be admitted freely that, in contrast to endemic goiter, the cause of the disease remains quite unknown" Hoover<sup>9</sup> averred "There is certainly no evidence of superfunction of the thyroid gland All the evidence seems to indicate that hyperplasia, so called, is evidence of incompetence of the gland and is associated with hypofunction rather than hyperfunction"

Our knowledge of clinical hyperthyroidism may be summarized by the statement that it is a complicated syndrome consisting of neurogenic, metabolic and glandular components There are present (a) a diminished storage of iodine in the thyroid gland, giving rise to hyperplasia, (b) a collection of sympathomimetic symptoms and (c) a general increase in the catabolic processes, the latter alleviated temporarily by iodine therapy and more lastingly by thyroidectomy No one of the components of clinical hyperthyroidism is pathognomonic Increase in the catabolic processes may occur in conditions unassociated with disturbances in the thyroid gland or the involuntary nervous system Sympathomimetic manifestations may be present with or without alterations in the thyroid gland or the basal metabolic rate Thyroid hyperplasia may occur in otherwise normal individuals, and in patients with an elevated or diminished basal metabolic rate

The complete clinical picture of hyperthyroidism consists in the simultaneous presence of the three abnormalities The autonomic imbalance precedes and is the precursor of hyperthyroidism When the catabolic phenomena are superimposed the clinical picture of hyperthyroidism is complete When the catabolic process has abated the autonomic imbalance persists and somehow, somewhere in the pathogenesis of this process there enters the exciting factor of a psychosomatic relationship that seems to be related to the phylogenetic approach to what we call civilization

#### DIAGNOSIS

Frank hyperthyroidism seldom presents difficulty in diagnosis Sympathomimetic manifestations and evidences of increased catabolism,

resulting in loss of weight and strength despite normal or increased alimentation, suggest examination of the thyroid gland, and estimation of the basal metabolic rate The therapeutic test of the response to iodine furnishes complete confirmation that clinical hyperthyroidism exists

Since determination of the basal rate requires the cooperation of patients who, because of their illness, find difficulty in offering the ideal tranquility so essential to the test, a strictly objective diagnostic measure has been sought Goetsch<sup>46</sup> attempted to utilize the adrenalin response for this purpose The presence of the adrenalin sensitivity in approximately 25 per cent of normal individuals and in a greater proportion of those with autonomic imbalance resulted in the abandonment of the Goetsch test More recently Shorr<sup>47</sup> attempted to employ for diagnostic purposes the disturbance in creatin metabolism King and Sohval<sup>10</sup> question the specificity of the metabolic disturbance since it was demonstrable in normal individuals, in patients with autonomic imbalance, and might be occasionally absent in patients with frank hyperthyroidism The latter investigators concluded that "clinical judgment surpasses in value any of these laboratory aids "

It should be a comparatively simple matter to differentiate patients with clinical hyperthyroidism from those with simple thyroid enlargement whether diffuse or nodular, hyperplastic, colloidal or adenomatous Simple thyroid enlargement is unassociated with sympathomimetic activity or an elevation of the basal metabolic rate, even when an anxiety state of "goiterophobia" is engrafted on the anatomical defect

Patients with autonomic imbalance are all too frequently treated as sufferers from hyperthyroidism Clinical differentiation should be simple on the basis of the long standing history in simple autonomic imbalance, the absence of clinical evidence of increased catabolism and the normal basal metabolic rate Elevation of the basal rate determined under ideal conditions and confirmed by repeated tests, which sometimes requires institutionalization of the patient, suggests the transition from simple autonomic imbalance to true hyperthyroidism

Patients with autonomic imbalance who dwell in a goiter belt and present the combination of sympathomimetic symptoms and a lump in the neck, with or without goiterophobia, are almost certain to be told sooner or later that they suffer from a *forme fruste* of hyperthyroidism or a true clinical hyperthyroidism, particularly if the goiter is nodular, suggesting the presence of so-called toxic adenomata Prophylactic thy-

roidectomy may be strongly urged. This procedure, in my opinion, is needless and unjustified. Determination of the basal metabolic rate is here of inestimable value for it will be normal in the absence of clinical hyperthyroidism, despite the association of autonomic imbalance, endemic goiter and goiterophobia.

Psychotic patients in manic phases, such as occur in the agitated depressions and the manic depressive states, may present a picture suggesting hyperthyroidism. It is impossible to determine the basal metabolic rate under these circumstances. It may require a prolonged period of study and a fine sense of clinical values to differentiate the two conditions. The therapeutic response to iodine is an important differential.

The diagnostic difficulties aforementioned deal with conditions in which clinical hyperthyroidism is erroneously diagnosed. A more serious error is the failure to recognize occult hyperthyroidism, in patients presenting atypical manifestations. Occult hyperthyroidism occurs most commonly in older patients who rarely present exophthalmos and whose sympathomimetic manifestations may be mild and unrecognized. To add to the diagnostic dilemma the thyroid enlargement may be negligible. The presence of the thyroid tumor may be missed if the swelling is retrosternal, intrathoracic or hidden beneath the muscles of the neck. If the thyroid tumor is of long duration its importance may be discounted in the interpretation of the more recent symptomatology. This group of older patients, presenting little exophthalmos and a long standing thyroid tumor, correspond to Plummer's<sup>4</sup> group of patients with secondary hyperthyroidism or toxic adenomata. The presenting symptoms in occult hyperthyroidism may be related to the circulatory system. Boas<sup>51</sup> has described a group of patients who seemingly suffered from an inexplicable hypertension. White,<sup>52</sup> whose practice is fairly limited to patients with circulatory disorders, found that 1 per cent were thyrocardiac invalids whose circulatory damage resulted from unrecognized and long standing hyperthyroidism. Another group with occult hyperthyroidism present asthenia and loss of weight. Malignant disease is suspected and the diagnosis of clinical hyperthyroidism may be overlooked. A notable feature of surgical therapy in occult hyperthyroidism, particularly in those with thyrocardiac manifestations, is the tolerance to staged operative procedure. Patients whose circulatory status would seem to indicate desperate risk often progress with amazing and gratifying equanimity.

It is a wise precaution to exclude active tuberculosis in every instance of suspected hyperthyroidism. Sympathomimetic manifestations are commonly encountered in patients with incipient tuberculosis. The febrile process, due to the infection, causes elevation of the basal metabolic rate. Temperature records should be written at four hour intervals for at least forty-eight hours. Careful examination of the chest, including radiography, must be performed if serious errors are to be avoided.

#### THE CLINICAL TYPES OF HYPERTHYROIDISM

No two patients with hyperthyroidism present symptom-complexes that are exactly similar. Stated positively, each patient with hyperthyroidism presents an individual symptom-complex. Plummer<sup>4</sup> believed that the clinical types were caused by alteration in the thyroid molecule. He differentiated between true hyperthyroidism resulting from an increased output of the normal thyronin molecule and a second type of hyperthyroidism due to an increased output of an altered thyroid molecule. In primary hyperthyroidism the patients were younger. Exophthalmos was common. The thyroid gland was diffusely enlarged. The history of metabolic disturbance was of relatively short duration. The response to iodine was favorable and the suggested surgical procedure was the approach to subtotal thyroidectomy. Those with toxic adenomata were in the older group. Exophthalmos might be negligible or absent. The history was of long duration. The thyroid enlargement presented isolated nodules, presumably toxic adenomata. The response to iodine was variable and might even be noxious. The operative procedure was removal of the adenomatous nodule without necessarily reducing the surrounding non-tumor tissue.

The hypotheses on which this differentiation was based have never been proven. It is my belief that the variations result from the altered response of the individual end organ to a fundamentally constant metabolic disorder. In animals, the response of the vascular system to a sympathomimetic drug produces an individual reaction picture that is as characteristic as the finger print. The reaction picture of each animal is always identical provided the sympathomimetic stimulation is the same. So too in clinical pharmacology, the response of each patient to an injected sympathomimetic drug, such as adrenalin, is always identical and always individual. In clinical autonomic imbalance the "reaction picture" is individual and identical. The individual reaction picture in

clinical hyperthyroidism is the result not of differences in the deranged physiology but of the response of the individual tissue to a unitarian disorder. The practical importance of the unitarian concept dwells in management. If Plummer's hypotheses are accepted, the primary and secondary cases of hyperthyroidism must be managed differently both medically and surgically. If the unitarian concept is accepted, the management of all patients is identical. Iodides are never contraindicated and may be given to each patient with a reasonable prospect for a successful therapeutic result. The surgical procedure is never to be concerned solely with adenomatous nodules but is directed to the approach to subtotal removal of both tumor and non-tumor tissue.

### CLINICAL FEATURES

The obvious clinical features of hyperthyroidism need no special emphasis before this audience. A few characteristics warrant brief comment. Hyperthyroidism occurs most commonly in civilized society. It is frequently familial and is more common in women than in men, though men present the more severe manifestations of the disease. Professional and sedentary workers are more commonly afflicted than manual laborers. The disturbance occurs most often in early adult life when strife and tension are greatest. A disproportionate number of Jews are afflicted—a disparity which is also present in the incidence of diabetes mellitus. Focal infection, particularly in the upper respiratory passages and most commonly in the sinuses and tonsils, plays a dominant role in the initiation of exacerbations and occasionally in the production of toxic storms.

The hyperthyroid patients lack resistance both physically and mentally. They are prone to develop any current infectious disease. The combination of nervousness, asthenia and muscular dystrophy produces frequent accidents, and social stress and conflict.

Periarthritis of the shoulder joint, so-called "frozen shoulder," occurs with undue frequency. Manipulative treatment under anesthesia gives complete relief.

### CLINICAL COURSE

Before the popularization of iodine therapy, Kessel and I<sup>53</sup> studied the spontaneous course of hyperthyroidism in order that we might more accurately evaluate therapeutic procedures. The spontaneous

course of hyperthyroidism in the majority of patients is toward recovery. The remissions are interrupted by exacerbations. The spontaneous cycles of exacerbation and remission may be of greater or lesser severity. They may be brief or protracted. In a certain proportion of individuals, vital organ damage, either circulatory or hepatic,<sup>74</sup> will arise, terminating in chronic invalidism or death. Occasionally the dreaded thyrotoxic crises will be experienced<sup>75</sup>—a large proportion of these terminating fatally.

### COMPLICATIONS

Mechanical symptoms arising from the pressure of the enlarged thyroid upon adjacent structures may complicate hyperthyroidism. Marked tracheal compression and distortion may occur without the production of subjective symptomatology. On the other hand, subjective complaints of dysphagia and dysphonia may be present, as the result of psychogenic factors (goiterophobia) with little or no objective evidence of pressure. In individuals who have had large goiters for many years, tracheomalacia may result. Tracheomalacia is a genuine surgical hazard. If its presence is suspected, the surgeon must be prepared to deal with tracheal collapse during the course of the thyroidectomy.

Malignant changes may occur in a goiter. Thyroid sarcomata are rarities. The diffusely hyperplastic gland rarely becomes carcinomatous. For the most part, carcinomata develop in adenomata. Statistics concerning the incidence of carcinomatous degeneration in adenomata vary according to the criteria of malignancy employed. Many of the histologic phenomena associated with malignancy may be observed in benign hyperplasia of the thyroid gland. If epithelial changes, without vessel invasion, be accepted as evidence of malignancy, then carcinoma of the thyroid is relatively frequent, reasonably benign and amenable to surgical therapy and irradiation. If the criteria of malignancy includes the phenomena of invasion of vascular structures, infiltration beyond the capsule or evidence of metastases, thyroid malignancy is relatively rare, highly malignant and therapy is all but futile.

Thyroid apoplexy may complicate hyperthyroidism. The rupture of an artery is uncommonly seen in diffusely hyperplastic glands but occurs more often in old cystic goiters with markedly sclerosed vessels. Thyroid apoplexy is one of the few painful thyroid afflictions. It is readily diagnosed, if suspected. Therapy may be expectant since the

thyroid capsule will act as a hemostatic

Vital organ damage occurs in individuals with long standing hyperthyroidism Marine<sup>16</sup> has called attention to the incidence of hepatic cirrhosis Cardiac hypertrophy and dilatation with myocardial and coronary changes may develop These may terminate in circulatory failure, producing the clinical picture of the thyrocardiac invalid

The most characteristic and ominous complication is the acute crisis<sup>55</sup> The thyrotoxic crisis consists in tempestuous exacerbation of all preexistent symptoms and, in addition, a febrile reaction of non-inflammatory origin The febrile reaction may be low grade or it may constitute an alarming and even fatal hyperpyrexia Characteristic of the acute crises are the alarming tachycardias and paroxysmal cardiac irregularities The neurological manifestations may consist either in agitation to the point of mania or collapse and coma

The origin and explanation of these crises are even more obscure than those of hyperthyroidism itself Crises may occur in individuals with mild evidences of hyperthyroidism, as well as those who are severely ill I observed a crisis in a cretin The crisis may occur without provocative cause, it may follow an acute emotional upset, an infection, or a surgical procedure, which need not necessarily involve the thyroid gland The crisis may occur after an appendectomy or tonsillectomy, or the trauma of an accident If the crisis follows thyroid surgery, the procedure may be one that is technically simple, as a ligation, or one of great magnitude, such as subtotal thyroidectomy The thyroid crises are as unpredictable as they are violent They constitute a constant threat in prognostication Their incidence has been greatly reduced as the result of iodine therapy

#### MANAGEMENT

The management of the individual patient with hyperthyroidism is a problem that has many facets Each patient presents a unique situation, hence management must be individualized

The constitutional autonomic imbalance that underlies the clinical picture of hyperthyroidism is not amenable to specific therapy Preparations of belladonna, ergot and quinine have been suggested and employed The use of belladonna is pharmacologically incorrect, since its paralyzant effect is upon the vagus rather than the thoraco-lumbar system Quinine has no specific action on the involuntary nervous system Though widely used, it serves no useful function Ergot, and

more specifically ergotamine tartrate, is theoretically indicated. In practice, however, these drugs have been disappointing. We possess no modality that can successfully alter the tonicity of the thoraco-lumbar system.

The management of hyperthyroidism begins with the attempt to eliminate the factors that tend to precipitate exacerbation. The most important of these is psychic trauma. Commonly, the psychic insult is characterological or situational. It would be impracticable to summon a trained psychiatrist to aid in the solution of each clinical problem. Commonly the internist, or preferably the general practitioner, is aware of the psychic disturbance. A sympathetic understanding, patience and a desire to suggest social and familial adjustments will usually suffice to diminish the burden. The cooperation of the family, fellow workers or employers may be enlisted. General hygiene may be corrected so as to permit more rest. The friction of every day life may be diminished by kindly and thoughtful advice.

Where the psychic trauma is more deeply seated, the help of a trained psychiatrist is advisable, if not imperative. Psychiatric consultation should be postponed until the metabolic abnormality has been corrected.

Focal infection, as the excitant cause for exacerbations, must be judiciously managed. In the attempt to eradicate foci, particularly in the sinuses or tonsils, it should be remembered that the thyrotoxic crisis may be precipitated by operative interference anywhere in the body. Consequently, it is wise to postpone tonsillectomy, for example, until after thyroidectomy has been performed. If it becomes necessary, with the thyroid intact, to eradicate a focus, the same type of preoperative treatment as for thyroidectomy is to be employed.

The management of the catabolic excess includes both specific and non-specific therapeutic measures.

The non-specific management of the exacerbation requires removal of the patient from his environment and institutionalization in order to procure mental and physical relaxation. Except in the rarest of instances, where the home is so luxuriously equipped that complete isolation is possible, the patient with hyperthyroidism should be admitted for hospital care. Patients and friends, alike, protest against hospitalization and suggest compromises, such as rest at home or in the country, but these alternatives invariably fail for one reason or another.

A high calory, high vitamin diet is maintained in order to spare the

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The management of hyperthyroidism begins with the attempt to eliminate the factors that tend to precipitate exacerbation. The most important of these is psychic trauma. Commonly, the psychic insult is characterological or situational. It would be impracticable to summon a trained psychiatrist to aid in the solution of each clinical problem. Commonly the internist, or preferably the general practitioner, is aware of the psychic disturbance. A sympathetic understanding, patience and a desire to suggest social and familial adjustments will usually suffice to diminish the burden. The cooperation of the family, fellow workers or employers may be enlisted. General hygiene may be corrected so as to permit more rest. The friction of every day life may be diminished by kindly and thoughtful advice.

Where the psychic trauma is more deeply seated, the help of a trained psychiatrist is advisable, if not imperative. Psychiatric consultation should be postponed until the metabolic abnormality has been corrected.

Focal infection, as the excitant cause for exacerbations, must be judiciously managed. In the attempt to eradicate foci, particularly in the sinuses or tonsils, it should be remembered that the thyrotoxic crisis may be precipitated by operative interference anywhere in the body. Consequently, it is wise to postpone tonsillectomy, for example, until after thyroidectomy has been performed. If it becomes necessary, with the thyroid intact, to eradicate a focus, the same type of preoperative treatment as for thyroidectomy is to be employed.

The management of the catabolic excess includes both specific and non-specific therapeutic measures.

The non-specific management of the exacerbation requires removal of the patient from his environment and institutionalization in order to procure mental and physical relaxation. Except in the rarest of instances, where the home is so luxuriously equipped that complete isolation is possible, the patient with hyperthyroidism should be admitted for hospital care. Patients and friends, alike, protest against hospitalization and suggest compromises, such as rest at home or in the country, but these alternatives invariably fail for one reason or another.

A high calory, high vitamin diet is maintained in order to spare the

tissues from the ravages of the excessive catabolism Sedative therapy by day and the hypnotics at night, assist in muting the nervous system

Professional nursing care, at least during the day, is almost mandatory An intelligent, sympathetic and cheerful nurse should be chosen She should be taken into the confidence of the physician, particularly concerning situational difficulties that have given rise to conflict between patient and relatives She may often tactfully manage the visitors who might otherwise be disturbing

The patient must not be permitted to chafe through idleness A daily schedule should be rigidly followed This schedule may be completed by hydrotherapy, occupational therapy and visiting by appointment A haphazard conduct of the sick-room will defeat the purpose of the rest cure The radio, for example, may be used for a limited time Under these circumstances it is quieting and sedative provided that amusing programs are chosen If turned on casually and left on indefinitely, it becomes a nuisance

For the specific management of the exacerbation, an infinite variety of therapeutic measures has been suggested Many of these have previously been discussed They include drugs such as belladonna, quinine and the ergots, glandular preparations such as thymus extract, adrenal cortical hormone, the principles of the male and female extracts such as estrone and testosterone and anterior pituitary extracts None of these possesses any specific therapeutic value Any improvement noted is probably a manifestation of the spontaneous remissions characteristically seen in the disease

Roentgen therapy has been widely used for the control of the exacerbation X-ray treatments of the thymic and anterior pituitary regions are certainly of no specific value Irradiation of the thyroid gland has been employed by many workers, notably Means and Holmes,<sup>56</sup> and is still widely utilized Hyperplasia of the thyroid gland is in no way altered by irradiation Kessel and I could find no appreciable difference in the course of patients treated by "skillful neglect" and those who had been irradiated Whatever benefits follow roentgen therapy of the thyroid gland result either from spontaneous remission or psychotherapy—the latter a potent non-specific factor in all types of physical therapy If the x-ray therapy has any place in the management of hyperthyroidism, its use may be reserved for patients ineligible for thyroidectomy If employed in those in whom thyroidectomy is

indicated, irradiation therapy, in my opinion, may be objectionable. The course of roentgen therapy delays the indicated operative procedure which then may be made technically more difficult by the increased fibrosis and vascularity of the irradiated tissue.

The re-discovery by Henry Plummer<sup>57</sup> of the amazingly specific effect of iodine in the treatment of hyperthyroidism constitutes one of the greatest of therapeutic achievements. Iodine may be given by mouth, inunction, injection or inhalation. The preparation may be organic or inorganic. The dosage is conventionally 5 to 10 drops of Lugol's solution three times a day. We are as ignorant of the correct dosage of iodine as we are of the mechanism by which the effect is obtained. Iodine should be given to every patient, whether of the so-called primary or secondary type, whether the thyroid gland is diffusely enlarged or adenomatous. The alleged contraindication to the use of iodine in so-called toxic adenomata has already been discussed. The specific effect of the drug is not dependent upon the histology of the thyroid gland.

Iodine therapy should be initiated immediately after the diagnosis is established. The response to the iodine may be used as a therapeutic test. If patients are to be institutionalized the drug should be withheld until the patient is admitted to the hospital lest the improvement lead to the belief that ambulatory therapy is possible.

The iodine reaction in hyperthyroidism consists in an extraordinary amelioration of symptoms. The effect may be measured by the diminution in the tachycardia and the fall of the basal metabolic rate. The relief of symptoms is initiated within twenty-four to forty-eight hours. Normality may be approached in two to ten days.

The immediate and dramatic therapeutic result does not occur in all patients. Occasionally the basal rate will be unaltered or it may actually increase. Many believe that these failures represented some altered reaction. The terms "iodine-fast"<sup>58</sup> and "iodine exacerbation"<sup>59</sup> have been employed to describe such instances. It is my own belief that the response to iodide in hyperthyroidism is always qualitatively the same. The quantitative differences depend upon the phase of the disease that is present during therapy. If the drug be administered at the onset of an exacerbation its effect will not be as obvious and dramatic as it would be if the patient were at the height of an exacerbation or at the beginning of a remission. The iodine effect is the sum of the specific action of the drug as modified by the violence of the exacerbation. If the patient fails

to improve with iodine therapy or the symptoms actually increase, not only should the drug not be stopped but increased dosage may be employed whilst further search is made for the continued operation of provocative exciting factors particularly in the psychogenic sphere

The duration of iodine effect is variable and dependent mostly upon the underlying character of the disturbance in the particular patient. Many individuals with but slight evidences of hyperthyroidism may be more or less indefinitely maintained at normal by the continued use of the drug. Those, however, with moderate or severe hyperthyroidism whose spontaneous course is characterized by frequent and violent exacerbations may be held in a "compensated" state only long enough to permit them to be prepared for surgical procedure. Parenthetically, it may be stated here that the indications for operative interference should not be influenced by the iodine response. If surgical intervention is to be part of the therapeutic program a favorable iodine response must not alter the decision.

Limitation of the use of iodine to preoperative preparation is erroneously conceived, since many patients with mild disturbance may be carried along indefinitely by the use of the drug. The therapeutics of iodine in hyperthyroidism is a relatively simple problem that has been complicated by fanciful hypotheses, having to do with iodine fastness, iodine exacerbation, and allegedly qualitative differences in response where adenomata are present.

The mechanism by which the iodine effect is obtained is completely unknown. *A priori*, one would expect iodides to be contraindicated and, indeed, from the writings of Troussseau<sup>60</sup> to the notable contributions of David Marine<sup>61</sup> this viewpoint was current in medical practice. It remained for Marine to point the way for iodine therapy in hyperthyroidism and for Henry Plummer<sup>4</sup> to demonstrate its value practically and popularize its use.

While conservative therapy, including the use of iodine, will almost invariably produce a remission, exacerbations may be surely anticipated when the patient is returned to his normal environment and subjected to the stress and strain of existence.

Subtotal thyroidectomy offers the patient the quickest return to social and economic restitution and a minimal risk of later exacerbation. With the exception of relatively wealthy patients who can afford to be pampered and coddled over a long period of time, the mild cases

controlled by iodine and those individuals who are constitutionally opposed to surgery, it is my opinion that every patient with hyperthyroidism should be subjected to a thorough-going subtotal thyroidectomy

The time to operate is to be determined by the clinical course. If the preoperative therapy succeeds in an approximation of the restoration to normal, no great time should be lost. Where circumstances will permit, I am in favor of the "stealing" operation. The time for operation should not be disclosed to the patient, so that the immediate panic and anxiety are allayed. Oftentimes the surgical procedure must be initiated earlier when very anxious and excitable patients become increasingly worse due to the suspense of the anticipated procedure.

Each patient should have some form of basal anesthetic. This may be avertin by rectal instillation or a barbiturate such as Nembutal taken orally. The use of an indifferent enema and lactose capsules for several days may mislead the patient from realizing the significance of the administration of the basal anesthetic.

The choice of anesthetic is a matter that can be determined by surgeon and anesthetist, but the decision as to the type of operation is one that must be settled between the surgeon and the internist or practitioner. The staged operation has the lower morbidity and mortality. It should be a matter of policy that if either surgeon or internist thinks the operation should be staged, the more radical opinion should yield to the conservative opinion.

The decision as to the staging of the procedure should not be made at the operating table and more surgery than originally planned must not be done merely because things seem to be going well. I favor the staged operation for patients whose original basal rate was greater than a +40 per cent, for those who have lost a great deal of weight and whose asthenia has been profound, for those whose basal rate cannot rapidly be brought to within twenty points of normal, for those who are highly agitated, nervous, restless, for individuals whose skins are deeply pigmented, for older patients with definite evidences of vital organ damage either in the liver or the circulatory system, for those who have a persistent hypertension or who have had any type of mental disorientation, for any patient who has ever had circulatory failure.

The first stage of operation should rarely be less than a hemithyroidectomy. If ligations are done the surgeon is faced with the alternative of multiple operations or a very formidable second stage.

procedure. However, if the patient takes the anesthetic badly, if paroxysmal cardiac irregularity of an alarming degree develops, the operation must be stopped at whatever stage the difficulty may arise.

Postoperative treatment should be initiated in the operating theater or, at latest, immediately upon the patient's return to the bedroom. An intravenous drip of 5 per cent glucose in saline is to be started whether or not indications exist. After the first liter of fluid, the solution is changed to 5 per cent glucose in distilled water since it is unwise to overload the patient with salt. Iodine is to be given either directly into the drip, by rectum or, if the patient is cooperative, by mouth. Again, the dosage is difficult to estimate but it is common practice to use daily from  $\frac{1}{2}$  to 4 cc of Lugol's solution for the first few postoperative days. The drip is to be maintained until the patient is wholly cooperative and well able to swallow fluids.

Many alarming complications may occur in the first few postoperative days. The most serious of these is the crisis with or without paroxysmal cardiac irregularity. Under these circumstances, there is invariably an elevation of temperature, as has previously been described. The vast majority of these postoperative crises are transitory and benign. Expectant treatment with sedatives or narcotics with continued intravenous administration of glucose and fluids will usually suffice. In the management of the postoperative crises, it is to be remembered that many patients with hyperthyroidism exhibit idiosyncrasy to morphine and that they are apt to vomit and become more agitated from the drug. The use of hypnotics such as the barbiturates and paraldehyde is considerably safer.

When the temperatures become excessive in the crises, that is beyond  $104^{\circ}$  F., antipyretic measures should be employed. These include sponges, packs, and the use of the coal tars. Kessel and I in instances of ominous thyrotoxic crises have used intravenous thyroxin in doses of 5 to 10 mgms. This has always been a measure of desperation, based on the possibility that the removal of the thyroid tissue produced some type of insufficiency in the metabolic economy. In a few instances, we have had the clinical impression that a specific result was obtained. This measure, however, is not to be employed unless the situation is ominous and the patient progressing unfavorably.

In the vast majority of instances, patients with crises are over-treated and may actually suffer from their medication. Digitalis is truly contra-

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## HYPERPARATHYROIDISM \*

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**E**volution of the Concept and Definition of Hyperparathyroidism It is now almost fifteen years since a case of Recklinghausen's bone disease was treated for the first time on the supposition that it might be based upon parathyroid hyperfunction The surgical history of this case is both illuminating and somewhat ironic, as will be indicated later on At any rate, the dramatic though temporary improvement which Mandl<sup>1</sup> obtained by removing a parathyroid adenoma from the subject in this case turned out to represent the cue to a significant clinical advance It is true that pathologists<sup>2</sup> had already noted the common presence of a parathyroid adenoma in cases of so-called "generalized osteitis fibrosa cystica" of Recklinghausen However, they had not hitherto fully grasped the pertinent causal connection between the skeletal alterations and the parathyroid lesion

The aforementioned clinical advance was concomitant with the development, by Hanson<sup>3</sup> and by Collip,<sup>4</sup> of chemical methods for the preparation of potent parathyroid extracts The experimental approach to the question of parathyroid hyperfunction thus also became possible Collip found that by injection of his extract (parathormone) he could raise the serum calcium level of normal dogs He was further able to prevent the onset of, or abolish, in dogs, the hypocalcemia and tetany of parathyroprivia—manifestations first interrelated by MacCallum and Voegtlin<sup>5</sup> in 1909 In addition, Greenwald and Gross<sup>6</sup> found that in dogs the hypercalcemia caused by parathormone was associated with an increased excretion of calcium and phosphorus through the urine Furthermore, Albright and his colleagues<sup>7</sup> demonstrated that the effects of the injection of parathormone in man were similar to those in dogs In regard to the blood, they noted that small doses of parathormone depressed the inorganic phosphate level, and raised the calcium level, of the serum

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In collaboration with Bodansky and Blair,<sup>8</sup> I was able to show in addition that in various susceptible animals the repeated injection of parathyroid extract induces bone lesions analogous in many respects to those seen in Recklinghausen's disease.

Meanwhile, cases confirming the dramatically beneficial effects of removal of a parathyroid adenoma in this disease were accumulating from many sources.<sup>9</sup> The cases in question also showed that, like the experimental injection of parathyroid extract, in dogs and human subjects, the disease tends to be associated with a rise in serum calcium, a drop in the inorganic serum phosphate, and an increased excretion of calcium and phosphorus in the urine. Altogether, then, by about 1931, the principal links in the chain of evidence for the idea that Recklinghausen's disease of bone is based upon parathyroid hyperfunction had been forged and connected.

The demonstration of this causal relationship between Recklinghausen's disease and an offending parathyroid adenoma finally destroyed the already waning theory of Erdheim,<sup>10</sup> that parathyroid enlargement appearing in association with bone disease should be regarded as secondary to, and compensatory for, the bone changes. On the basis of the Erdheim hypothesis, Mandl himself, in the case which later became classic, resorted at first to homoplastic parathyroid transplantation. However, when he found that the condition of the subject was aggravated by this procedure, he used the opposite one of searching for, and removing, the enlarged parathyroid known usually to be present in these cases. Nevertheless, though the Erdheim theory has had to be abandoned, we should not forget that Erdheim was a pioneer in appreciating the importance of parathyroid-skeletal interrelationships.

Guided especially by the recent work of Castleman and Mallory,<sup>11</sup> the present tendency is to classify parathyroid enlargement in general as taking the form of either a neoplasia or a hyperplasia. Parathyroid neoplasia, which is relatively uncommon, usually affects a single gland, though occasional instances of tumorous or neoplastic enlargement of two glands have been encountered. Parathyroid hyperplasia affects all (that is, the theoretical four) parathyroids. Even if one or two of the glands are not grossly enlarged, they at least show microscopic evidences of hyperplasia. Parathyroid hyperplasia has been subdivided into primary (or idiopathic) and secondary hyperplasia. This division is made on the basis of absence or presence, respectively, of some plausible

instigating factor, and also on the basis of certain differences in histologic detail In Recklinghausen's disease of bone, the parathyroid disorder is usually a neoplasia, though occasionally an idiopathic hyperplasia

Secondary parathyroid hyperplasia is encountered not infrequently in rickets and osteomalacia and sometimes also in Paget's disease of bone, carcinoma extensively metastatic to the skeleton, multiple myeloma, Cushing's syndrome, etc It is commonly found in cases of chronic renal insufficiency In fact, secondary parathyroid hyperplasia is found more regularly, and is more pronounced on the whole, in connection with chronic renal insufficiency than with any other condition in which it has been reported

It is the clinico-pathologic effects of parathyroid hyperfunctioning that represent what we shall mean by hyperparathyroidism It is the pathology, the clinical aspects, and the differential diagnosis of hyperparathyroidism arising in association with neoplastic or idiopathic diffuse parathyroid enlargement that will mainly concern us for the rest of this paper Since we do not know what instigates the parathyroid hyperfunctioning in these cases, we can think of them as instances of primary hyperparathyroidism The question also arises whether, in cases manifesting secondary parathyroid hyperplasia, parathyroid hyperfunction ever becomes severe enough to induce pronounced skeletal and other tissue changes in its turn The answer to this question seems to be in the affirmative, notably in connection with long-standing chronic renal insufficiency associated with pronounced parathyroid hyperplasia secondary to the renal disease Indeed, recent observations have established unequivocally the existence of an important kidney-parathyroid inter-relationship The hyperparathyroidism appearing under such conditions may be regarded as a complicating or secondary hyperparathyroidism

*Incidence* Primary hyperparathyroidism, while not a common disease, is not rare Its incidence seems to be at least two or three times as high among females as among males It occurs most frequently between the ages of 30 and 60 While it is not uncommon at other ages also (notably between 20 and 30 years), it seems to be definitely rare below 10 years No racial, hereditary, dietary, or environmental factors in the incidence of the disease have been definitely established However, it seems worth noting in this connection that Goldman and Smyth<sup>12</sup> do report two cases appearing in the same family, one in a girl of 17 and the other in her brother of 23 Also, I have the impression

that the disease used to be more common 20 or 30 years ago than it is now, albeit it was then often misdiagnosed as osteomalacia, or senile osteoporosis or osteomalacia I have gained this impression from study of the pathologic material and notes of the late Professor Erdheim,\* having found such cases particularly abundant for this earlier period The material also shows that when female subjects suffering from the disease became pregnant, the disease was strongly aggravated

*Course of the Disease* The onset of the disease is usually insidious and its course protracted The subjects are likely to complain early of vague, aching pains, especially in the limbs, and of stiffness in joints The clinical manifestations may be misinterpreted for months or years Indeed, the presence of the disease is sometimes not suspected until the dramatic fact of a pathologic fracture leads to the diagnosis The way to the latter is also sometimes first opened up through the discovery of a bone swelling Indeed, I personally have seen two cases in which dentists had made the proper association between a so-called giant-cell tumor of a jaw bone and an existing hyperparathyroidism Furthermore, there are many cases in which renal symptoms, and notably those of renal calculus, are the presenting ones and the skeletal alterations are in the background or even equivocal Occasionally, gastrointestinal symptoms such as attacks of nausea and vomiting are prominent and even the presenting phenomena, if the skeletal alterations are not clinically obvious, may confuse the clinician as to the true nature of the condition

Unless the offending parathyroid tissue is removed, the disease usually progresses until the patient is hopelessly bed-ridden in consequence of pain, repeated fractures, and deformities (Figs 1, 2) There is wide variation in the speed with which this course is run In one of the cases which I studied from the Erdheim material it was completed in eight months, while in another it was completed in three years However, even three years represents a relatively short course, for many cases seen today in which the patients are not yet badly deformed already have a relevant history dating back longer than this Fortunately, the

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\* This is the personal material willed by the late pathologist, Professor Jakob Erdheim of Vienna, to his former assistant and friend, the late Dr Ernst Irennd, more recently of Los Angeles, and brought to this country by Dr Philipp Rezek, now of Miami, Florida It was bequeathed by Dr Freund to me, and I am now living it established at the Hospital for Joint Diseases as a museum to the memory of Professor Erdheim I wish to acknowledge this collection is the source of some of the pathologic material used in connection with this lecture

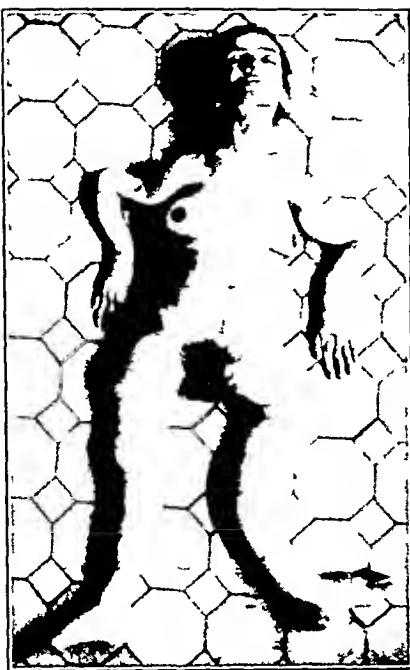


Fig. 1—Photograph of patient of 32-year-old woman, revealing deviation of the skeleton in connection with hyperthyroidism. Death occurred in 1925, a year which represents a transition in our understanding of the disease toward the prevention of such severe skeletal involvement.



Fig. 2—Photograph of the long bones removed from the lower limbs of patient shown above, in this case emphasizing their extreme curvature and irregular distension.

condition is now usually properly diagnosed and treated before it has advanced enough really to devastate the skeleton. If the condition is allowed to go unchecked, death ensues, usually in consequence either of uremia or of an intercurrent disease such as pneumonia.

*General Pathology of the Skeletal Changes.* More and more frequently, we now encounter clinical cases of hyperparathyroidism in which, even roentgenographically, there is still little if any evidence of skeletal involvement. These cases are picked up at this early stage because observers are now alert for the disease and because there are now established laboratory criteria for its diagnosis. Formerly, such cases were picked up only incidentally at autopsy, the subjects having died from some other cause. In cases of hyperparathyroidism with minimal skeletal involvement, the gross changes so far as the bones are concerned may consist merely of a slight porousness of the vertebral column, ribs, pelvis, and long bones.

Microscopically, in these cases with very slight skeletal changes, the bones show merely a mild degree of generalized osteoporosis and fibrosis. This stands out more clearly in some bones—notably the ribs, the femora, the jaw bones, and the bones of the vertebral column—than in others such as the bones of the hands and feet. The spongy trabeculae of the affected bones are found perforated by, and surrounded by, tracts of connective tissue (Fig. 3). The cortices of these bones show enlarged vessel canals containing abnormal amounts of connective tissue. On the walls of the trabeculae and vessel canals where the resorption has been going on, osteoclasts and Howship's lacunae are in evidence. In these cases, little if any new bone has yet appeared in the connective tissue that is replacing the original osseous tissue.

Progression of the disease in the skeleton is characterized by increasing resorption of the original osseous tissue and increasing replacement of it by connective tissue in which new bone is formed. However, the substitute bone, which is rather primitive histologically, tends to remain moderate in amount and not to be particularly rich in calcium. Eventually, in a severely affected bone, the internal architecture shows extensive modification and there may no longer be any vestige of original osseous tissue.

This status is approached through broadening and thickening, followed by merging of the tracts of connective tissue surrounding and replacing the spongy trabeculae (Fig. 4). In this way, large fibrous scars

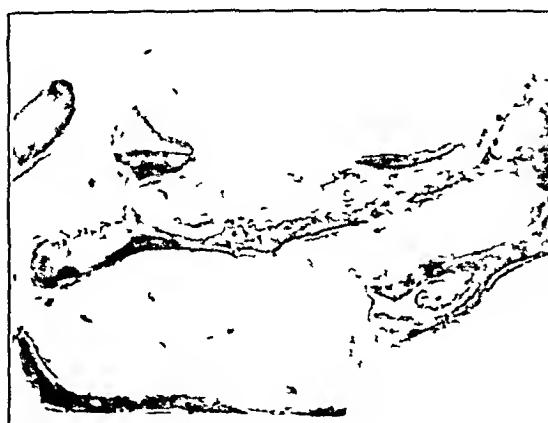


Figure 3



Figure 4

Fig 3—Photomicrograph  $\times 125$  from an early case showing dissection and perforation of the original trabeculae at the end of a long bone by tracts of connective tissue. Much of the intertrabecular marrow is still fatty, and as yet there is little if any evidence of new bone formation in the substituting connective tissue.

Fig 4—Photomicrograph  $\times 6$  from an advanced case, showing substantial replacement of the spongiosa at an end of a long bone by connective tissue and new bone which, in the lower left hand corner, can be seen to have formed a rather dense structure.

are formed in the place of the original spongiosa. Though connective tissue and new bone substantially or completely replace the original cortical bone, too, reactive periosteal new bone deposition is lacking except at sites of fracture. The cortical thickening which one occasionally encounters in a bone even without fracture can be shown to have taken place on its medullary side. In the transformed cortex and spongiosa one may encounter small or larger brownish fibrous scars representing the so-called brown or giant-cell tumors. Smaller or larger cysts may also be found, but these are by no means as common anatomically in hyperparathyroidism as the synonym, "generalized osteitis fibrosa cystica," would imply (Fig 5). In very severe cases, fractures, and the consequences which they entail in the form of hemorrhage, reactive callus formation, and malalignment complicate and confuse the anatomic picture in the different bones.

As to the distribution of the skeletal lesions, one would expect that since the action of parathyroid hormone upon the osseous system occurs through the blood stream and circulating tissue fluid, the bones would be evenly affected. As a matter of fact, in any given case, all do show involvement to some extent. They are by no means evenly affected,

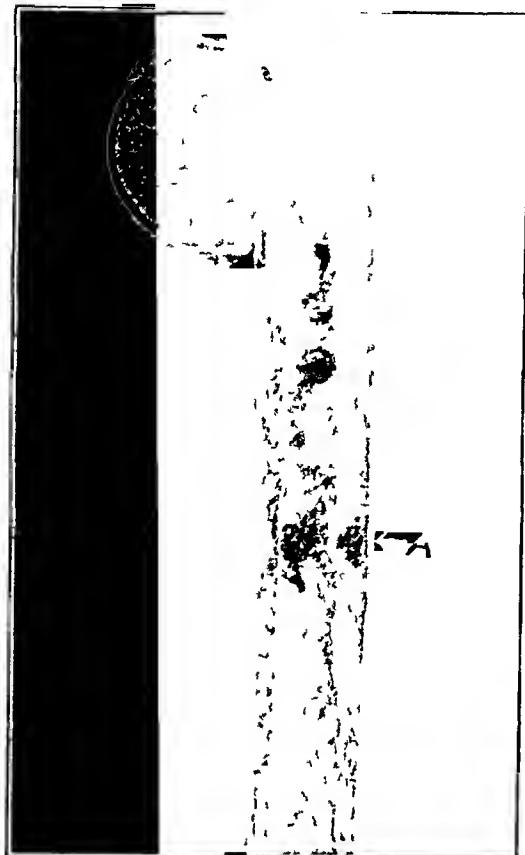


Figure 5

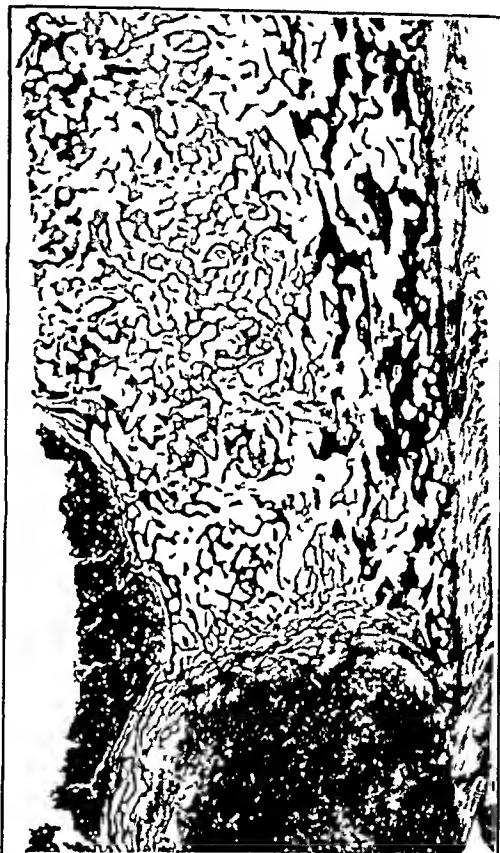


Figure 6

Fig 5—Photograph of humerus of a 19-year-old girl who had suffered from hyperparathyroidism. The deformity at the head-shaft junction developed at the site of a fracture. The major marrow cavity is intact and contains myeloid and fatty marrow. The shaft cortex is completely transformed. At A, the cortex is occupied almost throughout its thickness by a "brown" tumor.

Fig 6—Photomicrograph  $\times 6$  showing, on a larger scale, part of the brown tumor and cortex above it from the humerus pictured in Fig 5.

however. On the whole, it is those bones and bone regions which are subjected to the strongest functional stress and strain that are the most likely to be seriously implicated in hyperparathyroidism. The tendency toward pronounced involvement of the long tubular bones and the vertebral column, for example, becomes understandable on this basis. Nevertheless, there may be discrepancies, in the degree of involvement, between two bones (such as the femora) which, in theory, would be expected to be equally implicated. Such differences may logically be

attributed to the presence of special complicating factors such as infractions or fractures, or the favoring of one side at the expense of another in such a way that the latter would be more likely to develop pronounced lesions. The importance of functional trauma in the localization of the skeletal lesions is especially striking in the case of the terminal phalanges, which, in contrast to the middle and basal phalanges, are likely to undergo particularly severe changes leading to clubbed fingers.

Even when the skeletal lesions are far advanced, the fully developed erupted teeth do not become involved in the general decalcification, although they may fall out in consequence of involvement of the jaw bones. Indeed, as Thoma<sup>13</sup> has shown, these teeth may even be hypercalcified. The developing teeth in man tend to show pronounced defects in dentin formation. In conformity with this finding, Schour and Ham<sup>14</sup> noted that in rats suffering from acute hyperparathyroidism the newly forming dentin of the incisor teeth may show deficient calcification.

*Cysts and Brown Tumors.* The nature and pathogenesis of these lesions, and their significance in the total skeletal picture of hyperparathyroidism present very complex problems. Anatomically, gross cysts and tumors are much less frequently encountered than the generally prevalent concept of the disease would lead one to expect. It is true that even in relatively early cases the bones may show cyst-like shadows roentgenographically. However, there is no proof that these shadows do not represent merely fibrous foci which have caused defects in the cortex or in the spongiosa and cast cyst-like shadows without actually being cysts. Indeed, this can be deduced from general experience with solitary bone lesions casting shadows suggesting cysts. On surgical exploration, these shadows very often turn out to represent merely areas of cortex or spongiosa which have undergone partial or complete replacement by cartilage, by fibrous tissue, by granulomatous tissue, etc. Furthermore, it is difficult to state with certainty how cysts form when they do form in cases of hyperparathyroidism. It seems likely that the majority of them represent merely fibrous masses or brown tumors which have undergone cystic degeneration after ischemia or hemorrhage.

The problem of the brown tumor in hyperparathyroidism is even more perplexing than that of the cyst. The impression which one obtains from the literature is that this lesion is more or less the exact counterpart of the solitary giant-cell tumor of bone. Our own findings are not in harmony, on the whole, with this conception. First of all, it

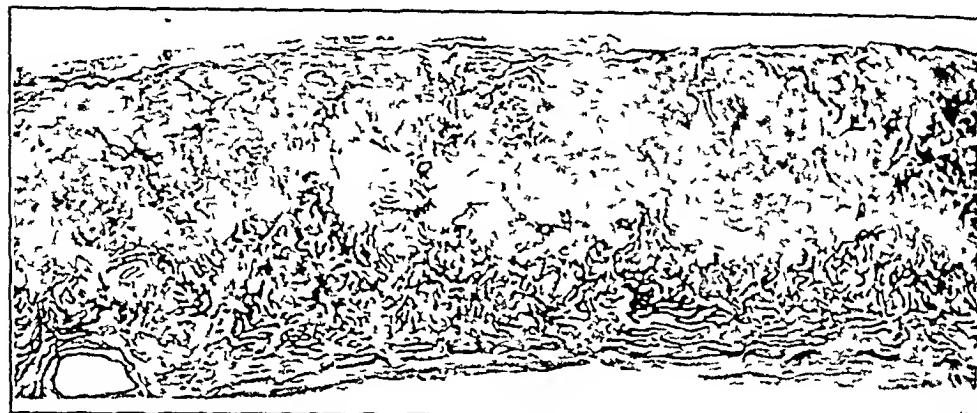


Fig 7—Photomicrograph  $\times 6$  of a rather completely transformed calvarium showing, in the upper part of the picture, a large fibrotic area which, in the gross, appeared brownish and which represents a so-called brown tumor.

seems clear that the histologic criteria for the diagnosis of solitary giant-cell tumor of bone ought to be kept much narrower than they are. The tendency to label as a giant-cell tumor any fibrous lesion or scar in bone which contains a few osteoclasts is to be deplored. It is this loose labeling that is responsible for the inclusion, in classifications of bone tumors, of such categories as "the osteitis fibrosa variant of giant-cell tumor" and "the giant-cell variant of osteitis fibrosa"<sup>15</sup>. Strictly defined, a solitary giant-cell tumor of bone is a true neoplasm which originates from mesenchymal connective tissue and in which the stromal cells and the giant cells show a close histogenetic relationship. Furthermore, in such a tumor, one should be able to see evidence that the giant cells are being formed from the stromal cells and also that the giant cells are abundant, are a significant part of the histologic picture, and do not resemble ordinary osteoclasts.

The brown tumors of hyperparathyroidism usually do not meet these criteria (Figs 7, 8). In them, as a rule, the giant cells are relatively sparse and quite closely resemble the osteoclasts present beyond their immediate area. Altogether, the brown tumors in hyperparathyroidism seem to represent small or larger fibrous scars containing some osteoclasts. However, the strict interpretation of them in this way encounters an obstacle. This is represented by the conditions obtaining when a brown tumor of a jaw bone erupts under the gum in the form of an epulis. In these cases, for some obscure reason, the histology of

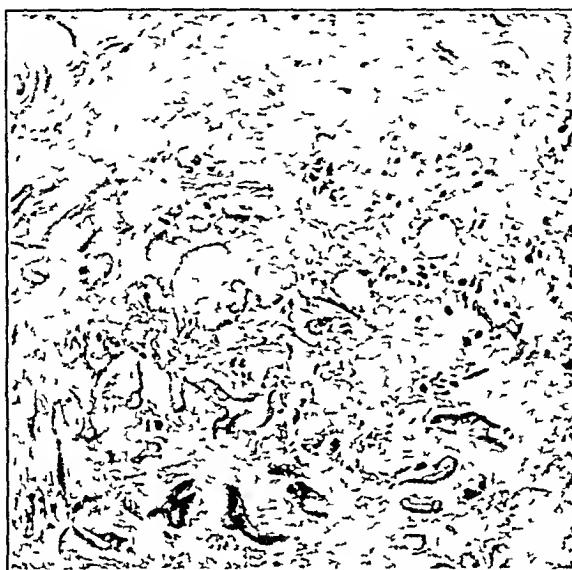


Fig 8.—Photomicrograph  $\times 100$  showing the details at the periphery of the lesion. The fibrous stroma and giant cells of the brown tumor are not essentially different from these elements in the neighboring tissue.

the lesion under the gum resembles that of solitary giant-cell tumor more closely than that of a brown tumor elsewhere in the bones in hyperparathyroidism. Through the courtesy of Dr Blum and Dr Guttinger, I have had occasion to examine pertinent tissue from the gum and jaw bone in two known cases of hyperparathyroidism with jaw involvement. In these cases, though the cytology of the epulis lesion resembled that of solitary giant-cell tumor, it appeared to me that that part of the brown tumor located in the jaw proper still retained some of the features of a fibrous scar with osteoclasts. It is difficult to understand why epulids in hyperparathyroidism should thus bear a special resemblance to solitary giant-cell tumors. Possibly it has something to do with functional trauma and hemorrhage into the lesion. Possibly also, even outside of jaw regions, such factors may have a similar influence upon a brown tumor. We can only say that our own material showed nothing of this kind.

*Pathology of the Extra-Skeletal Changes.* As has already been noted, the parathyroid abnormality in hyperparathyroidism may be of the

nature of an adenoma or of a hyperplasia. When the abnormality is adenoma formation, the tumorous growth is usually limited to a single gland. As often as not, the adenoma is composed almost solely of typical chief cells, and when it is not, it still contains some chief cells. When the abnormality is a hyperplasia, it involves the theoretical four glands, and the hyperplastic glands are composed of water-clear cells.

Aside from the parathyroids, the kidneys are the extra-skeletal tissues most likely to be affected in hyperparathyroidism. Indeed, with the parathyroid disorder as the apex of the pathologic triangle, the two important sides of it are skeletal lesions and renal lesions. Of the latter, renal calculi are among the commonest. Somewhat more than one-third of the cases of hyperparathyroidism presenting roentgenographic evidence of bone lesions also show renal calculi. Furthermore, the incidence of renal calculi is even higher if one includes cases of hyperparathyroidism which as yet do not show clear-cut roentgenographic evidence of skeletal involvement. For these reasons, determination of the serum calcium seems clearly indicated in all cases of renal calculus, and if this value is found above normal the skeleton should also be roentgenographed.

Nephrocalcinosis is another important, though much less common, renal complication, and may appear independently or in association with calculi. The calcium deposition is mainly peritubular and is likely to obstruct the tubules and interfere with their function. Kidneys damaged by the presence of calculi or nephrocalcinosis may also show evidence of superimposed infection in the form of pyelonephritis. Altogether, chronic renal insufficiency is very likely to appear. This in its turn probably increases the parathyroid hyperfunction and hence exacerbates the state of hyperparathyroidism. If the kidneys have been damaged irreversibly, the chronic renal insufficiency may exert its effects upon the parathyroid glands remaining after removal of an adenoma. Especially in cases with severe renal insufficiency, widespread metastatic calcifications may be present in many soft parts, including the subcutaneous tissues and arteries.

*Differential Diagnosis.* A number of conditions may present problems of differential diagnosis in relation to hyperparathyroidism. It is immediately helpful to remember that the latter disease is, after all, relatively uncommon. Because of this fact, in weighing whether a given obscure case is or is not one of hyperparathyroidism, the burden of

proof lies upon the affirmative side. The conditions whose manifestations sometimes raise this problem of differential diagnosis include adolescent rickets and osteomalacia, senile osteoporosis, carcinoma extensively metastatic to the skeleton, multiple myeloma, Paget's disease, and polyostotic fibrous dysplasia.

Before proceeding with the discussion of differential diagnosis, it seems advisable to consider the question of protracted renal insufficiency. In the latter condition, both in childhood and in adult life, hyperparathyroidism may be present as a complicating or secondary disorder even if renal disease is the underlying one. The pronounced osseous changes occurring in cases of renal rickets are well known and have been inadequately described. In fact, solely on the basis of histologic study of bone sections, it is usually not possible to tell whether one is dealing with a case of renal rickets or one of hyperparathyroidism. It is true that in the former condition one does not see the brown tumors and cysts, but these are not necessarily to be found in hyperparathyroidism either. Extensive osseous changes have also been observed in a few cases of chronic renal insufficiency in adults, in which they have usually been denoted as generalized osteitis fibrosa. In these cases there was pronounced enlargement of the parathyroids, such as one sees also in cases of renal rickets. Altogether, the osseous findings in these cases may be regarded as the adult equivalent of those noted in renal rickets of childhood. In the presence of such pronounced osseous changes, secondary hyperparathyroidism can safely be inculpated as a factor contributing to the causation of the bone lesions. Anderson<sup>16</sup> has recently reviewed the whole question of hyperparathyroidism in relation to renal disease.

Of further interest in regard to the relation of chronic renal insufficiency to the osseous system are certain findings which were recently noted by my former associate, Dr. Ginzler, and myself.<sup>17</sup> In the usual run of cases of chronic renal insufficiency revealing mild degrees of parathyroid hyperplasia at autopsy, we have routinely examined bones from various parts of the body. Our observations in regard to these cases may be summarized as follows. The bones, though usually not altered grossly, often reveal, on microscopic examination, mild but clear-cut fibroporotic changes in the spongiosa. In these cases, the spongy trabeculae show scattered resorption lacunae containing osteoclasts and connective tissue, and some of them may also present, here and there, deposits of new bone. Occasionally—and specifically when the renal

insufficiency has been very protracted—the bones will be found even grossly altered. In these cases, the spongiosa is close-meshed, and the trabeculae are thickened and distorted, so that altogether the skeletal condition amounts to an osteosclerosis. The microscopic observations indicate that the osteosclerosis has developed through gradual accretion of new bone, despite the alternation of reparative with resorptive processes that must have been going on for a long time.

Only Rutishauser<sup>18</sup> has described osseous changes sometimes rising to the level of osteosclerosis in patients with renal disease in whom secondary hyperparathyroidism was probably a factor, though only a subordinate one, in the development of the bone lesions. What probably underlies most of the bone changes in these cases is the chronic acidosis due to the renal damage.

We turn now to adolescent rickets and osteomalacia. We all know that adolescent rickets is by no means as common in the United States at present as it was thirty or even ten years ago. In fact, at our hospital, despite the high proportion of negroes in its ward and out-patient population, we practically no longer see cases of adolescent rickets. In the rare instances in which hyperparathyroidism appears in children, it may be mistaken for adolescent rickets. This is so because, like rickets, it tends to lead to generalized demineralization of the skeleton, widening of the epidiaphysial regions, deformation of the thoracic cage, coxa vara, and knock knees or bow legs. However, in view of the rarity of both genuine adolescent rickets and hyperparathyroidism, children now found presenting these skeletal abnormalities are more likely to be suffering from so-called renal rickets or idiopathic steatorrhea than from either of the other two disorders. Serum calcium and phosphorus determinations of course aid in the differential diagnosis. In cases of idiopathic steatorrhea the gastrointestinal history also sheds light. Furthermore, in cases of adolescent rickets, renal rickets, and idiopathic steatorrhea one does not find such roentgenographic bone shadows as would indicate the presence of cysts and so-called "brown tumors."

Genuine osteomalacia of adults—that is, the osteomalacia of calcium deprivation and added vitamin D deficiency—has always been rare in this country. This is the osteomalacia which is associated with repeated pregnancy or pregnancy of young girls and which is still endemic in parts of China and India. Occasionally, in this country, we do encounter a sporadic instance of non-puerperal bone softening which simulates genuine

osteomalacia but does not respond to the usual treatment for this condition. At any rate, in cases of osteomalacia, as contrasted with hyperparathyroidism, the serum calcium value is at most, barely up to the normal and is usually subnormal. Furthermore, in osteomalacia, the roentgenographs of the skeleton do not reveal the cysts and "brown tumors" not uncommon in hyperparathyroidism, nor are the bones usually as much rarefied as they are in an advanced case of hyperparathyroidism. In their general tenor, these remarks are true also in relation to nutritional and hunger osteoporosis.

Occasionally, senile osteoporosis, too, is mistaken for hyperparathyroidism. It may be worth mentioning, however, that I have seen definitely fewer instances of senile osteoporosis in recent years than I formerly saw. This fact seems to reflect the recent advances in our knowledge about nutrition, and the raised standards of care for the old. Of considerable aid in the differential diagnosis is the fact that in senile osteoporosis the serum calcium, phosphorus, and phosphatase activity values are normal unless fractures are present. In the presence of the latter, the phosphatase activity value may be found elevated but not, of course, the serum calcium value.

Cancer extensively metastatic to the skeleton sometimes also raises the problem of differential diagnosis, although confusion on this point can be easily avoided. The diagnostic difficulty is most likely to appear if, as happens in rare, extreme cases, the metastatic bone involvement is associated with a hypercalcemia. In any event, even if the primary growth is not clinically evident, there is one roentgenographic feature which can prevent the diagnostic error. This is the fact that in cancer, no matter how extensive the rarefaction of certain bones may be, or how strongly their appearance may suggest Recklinghausen's disease, other bones, and sometimes even parts of badly affected bones, will be found relatively normal roentgenographically. In Recklinghausen's disease, on the other hand, when some bones are badly affected, all the rest will be found at least somewhat altered.

Not infrequently, indeed, I have observed cases of multiple myeloma which have been misinterpreted, at least temporarily, as instances of hyperparathyroidism. I suppose it is the relatively common finding of a hypercalcemia in multiple myeloma that is at the bottom of this confusion. However, in the presence of this finding, further investigation of the blood will reveal a hyperproteinemia with an inversion of the

albumin-globulin ratio The latter finding should be immediately recognized as the cue to the presence of multiple myeloma Furthermore, multiple myeloma is characterized by the fact that the serum phosphatase activity tends to remain normal, no matter how extensive the skeletal involvement may be It is conceivable that if the serum phosphatase activity is measured at a time when numerous fractures are in the process of healing, this activity may be found slightly increased, but the increase does not attain the level that it usually shows in advanced cases of hyperparathyroidism In addition, it is well known that a good percentage of cases of multiple myeloma also show, sooner or later, a Bence-Jones proteinuria

Actually, a proper appreciation of the roentgenographic appearance of the calvarium in cases of multiple myeloma should suffice to prevent confusion with hyperparathyroidism, irrespective of the roentgenographic findings elsewhere The small punched-out areas of rarefaction in the calvarium are rather typical for multiple myeloma and are not found in hyperparathyroidism The rarefactions of the calvarium in Hand-Schuller-Christian's disease are usually much less numerous and much larger The so-called circumscribed osteoporosis of the calvarium found early in involvement of the skull in Paget's disease is also easily distinguishable, on the basis of the small number and large size of the rarefactions, from cranial involvement in multiple myeloma Finally, reference should be made to the hyperplastic parathyroids sometimes to be found at autopsy in cases of multiple myeloma I am inclined to think that the hyperplasia in these cases is secondary to the renal insufficiency so often developing in the course of the disease

Paget's disease should no longer ever be confused with Recklinghausen's The total picture—clinical, biochemical, and roentgenographic—is clearly different The pathologico-anatomic picture is also decidedly different One does not find, in hyperparathyroidism, the large circumscribed areas of rarefaction of the calvarium that are characteristic of the early stages of Paget's disease of the skull In uncomplicated cases of Paget's disease the serum calcium and phosphorus values are normal However, very rarely, one encounters a case of Paget's disease in which routine biochemical study reveals a definite hypercalcemia A few cases of this type have been subjected to exploration of the neck for a parathyroid adenoma, which indeed was found However, in these cases, the extirpation of the adenoma did not influence the course of the Paget's

disease. These cases must be interpreted as instances of Paget's disease complicated by hyperparathyroidism, or at least as instances of the coexistence of the two diseases in the same subject.

A condition which is frequently and unnecessarily misdiagnosed as hyperparathyroidism is "polyostotic fibrous dysplasia," which my colleague and associate, Dr. Lichtenstein,<sup>19</sup> named and recently described in detail, emphasizing especially its pathology. Clinical reference to the condition had previously been made under such names as "unilateral fibrous osteodystrophy," "unilateral Recklinghausen's disease," "disseminated osteitis fibrosa," "osteitis fibrosa in multiple foci," etc.

The condition is a skeletal developmental anomaly affecting several or many bones, with predominantly unilateral involvement. The affected bones show filling of their medullary cavities by gritty, grayish-white fibrous tissue containing trabeculae of newly formed primitive bone. Islands of cartilage may also be found in the fibrous tissue filling the marrow cavity. The condition apparently results from perverted activity of the specific bone-forming mesenchyme. It usually manifests itself in childhood or early adult life and evolves slowly, pursuing a protracted clinical course characterized by pain, deformity, and a tendency to pathologic fracture of affected bones. Precocious menstruation in girls suffering from severe forms of the disease has been described by Goldhamer,<sup>20</sup> by Borak and Doll,<sup>21</sup> and more recently by Albright and associates.<sup>22</sup> The presence of hyperpigmentation of certain areas of the skin, apparently due to excessive melanin content, has also been mentioned by Goldhamer and particularly stressed by Albright and his associates. The precocious menstruation and hyperpigmentation are apparently seen only in very severe cases whose clinical manifestations have begun very early in life.

It is probable that the precocious menstruation and other endocrine phenomena, manifested in only a small proportion of these cases, result from damage to structures at the base of the brain from involvement of underlying skull bones. Indeed, one exhibitor at this Fortnight is demonstrating several of these special cases under the heading of "A rare Endocrinopathy probably of Pituitary-Hypothalamic Origin." Another is showing a number of them under the heading of "A Syndromic characterized by Precocity in Females, Hyperpigmentation, and disseminated Osteitis Fibrosa." All these cases would fall into their proper place as instances of particularly severe polyostotic fibrous dysplasia with sec-

ondary phenomena due to damage of the base of the brain and possibly nerves. One should bear in mind that the great majority of cases of this disease show no such secondary phenomena and that indeed even the osseous changes may be limited to a few bones developing from a single limb bud.

It is because roentgenographically the affected bones appear widened, show thinned cortices, and often present appearances suggesting the presence of cysts that these cases are so often misinterpreted as instances of hyperparathyroidism. At least five or six cases of the seventeen which have come under my personal observation had previously been thus misdiagnosed and had consequently been subjected to a vain search for a parathyroid tumor. The fact that the lesions are unilateral or mainly unilateral and that the unaffected bones are normal should be enough to exclude hyperparathyroidism. Furthermore, the serum calcium value is normal in practically all cases of polyostotic fibrous dysplasia. Occasionally however, it may be slightly above the upper limit of the normal. For instance, it was 110 mg. in one of our cases.

*Treatment, Parathyroidectomy.* In principle, the treatment consists of surgical removal of the offending parathyroid tissue. When this is successful, the pathologic state is abruptly arrested and soon begins to be reversed. In fact, substantial healing of the skeletal lesions may be manifest within a few months, even to the point of great reduction in the size of cysts and brown tumors. On the other hand, deformities do not become spontaneously corrected to any great extent after they have once developed.

Churchill and Cope<sup>23</sup> and Lahey and Haggard,<sup>24</sup> among others, have discussed the surgical problems involved, and also describe technical procedures facilitating accession to aberrantly located enlarged parathyroids. In at least four out of five cases of hyperparathyroidism, the offending parathyroid tissue consists of a single parathyroid adenoma. Occasionally, two adenomata are encountered at operation, in which case both should be removed. However, there are also cases (such as that of Hellstrom<sup>25</sup>) in which, after the removal of one adenoma, the impermanence of the resultant remission of the symptoms forces one to the conclusion that another adenoma must have been present which was missed. In addition, there are cases in which the possibility exists that the second adenoma only developed some years after the first one had been removed. Indeed, this seems to have been what happened in Mandl's

original case. After having maintained remarkable improvement for a number of years, the subject suffered a relapse, and this was logically attributed to the development of another adenoma. The irony of the situation is that, on re-exploration, Mindlovitz was unable to find a second adenoma, the latter probably being aberrantly located.

If, as is the case sometimes, the hyperparathyroidism is being caused by idiopathic parathyroid hyperplasia instead of adenoma formation, the surgical treatment presents particularly knotty problems. This is so because all four of the glands may be hyperplastic and there is danger of intractable tetany if all four are removed. On the other hand, if all four are not enlarged, there is no assurance that the remaining gland or glands will not subsequently undergo hyperplasia and thus induce recurrence of the symptoms. Albright and associates<sup>7</sup> recommend that three of the hyperplastic parathyroid glands be removed and the fourth partially extirpated so that at most no more than about 400 mg of parathyroid tissue remains. In their experience, the effect of this procedure upon the state of hyperparathyroidism was to correct it permanently so far as present indications go. My experience with one case of this type, in which only two hyperplastic glands were removed, was that there was a rapid recurrence of all the manifestations of hyperparathyroidism within a few months. It has occurred to me that in such cases it might possibly also be advantageous to remove three of the parathyroid glands and all but a tiny fragment of the fourth and immediately transplant some of the parathyroid tissue into the abdominal wall. Here it would be easily available should removal of additional parathyroid tissue be indicated later on. In any event, in these cases, the surgeon must recognize the danger on the one hand of recurrence of the hyperparathyroidism from regrowth of the remaining stump and on the other of the development of intractable hypoparathyroidism from damage to the essential remaining tissue.

*Postoperative Complications and Precautions.* Hypoparathyroid tetany associated with the development of a hypocalcemia is a common postoperative complication. Often on the day following the operation, numbness and tingling—precursors of the tetany—already appear in the fingers and toes. Another postoperative complication which is common is oliguria. This usually corrects itself, however, after a few days. It may be noted that if, at the time of operation, advanced renal damage (nephrocalcinosis or pyelonephritis) exists, great danger of subsequent

death from uremia will remain

Immediately after parathyroidectomy, precautions should be taken to prevent the onset of tetany. Large amounts of soluble calcium salts given by mouth are often effective. Because of the rapidity with which calcium salts are eliminated after ingestion, it is also desirable to give them frequently. For instance, 4 grains of calcium lactate may be given every 2 or 3 hours during the day and perhaps somewhat less often during the night. When the presence of tetany makes prompt effects urgent, the intravenous injection of 10 cc of calcium lactate or gluconate may be necessary. If the administration of calcium by mouth does not adequately elevate the serum calcium, the desired result can be achieved through the supplementary injection of parathormone. To this end, 10 or 20 units of the parathyroid extract may be given several times daily for a while (subject to control by determinations of the serum calcium). In addition, the diet of patients suffering from latent tetany should be low in phosphorus. It may well be supplemented by large therapeutic doses of viosterol (60 to 90 drops, three times a day), or any of the more potent recently developed vitamin D preparations. This treatment should be cautiously continued for a number of weeks, by which time the serum calcium will probably have risen above the tetanic level. In intractable cases of hypoparathyroid tetany, homotransplantation of parathyroid tissue gives some promise of success.

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## GENERAL CRYMOTHERAPY A SYMPOSIUM\*

## FOREWORD

*In July 1939, it was decided to make a clinical investigation of local and general crymotherapy at the Lenox Hill Hospital, New York. Accordingly a specially equipped, thermostatically controlled, air-conditioned room with a capacity of two beds was constructed. Intern and nursing personnel were thoroughly familiarized with clinical and technical details of general crymotherapy. On October 17, 1939, the first patient was subjected to the so-called artificial hibernation. This symposium is an account of four months' experience with this procedure.*

*Rationale and Description of Method Selection of Cases  
Conditions Treated*

JOHN C A GERSTER

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**T**HE originators of the so-called "Artificial Hibernation Treatment" (Crymotherapy) were Temple Fay and Lawrence Smith of Temple University Medical School, Philadelphia.

Fay, in the course of taking routine skin temperatures as part of standard neurological examinations, found that the skin over the breasts was constantly several degrees warmer than the skin above and below this region, furthermore, the skin of the extremities below the elbows and below the knees was regularly from 6° to 20° F cooler than that of the rest of the body. This finding he correlated with the well-known fact that in generalized carcinomatous secondary involvement of the bony skeleton, the bones of the extremities below the elbows and below the knees were rarely, if ever, affected. Fay thought that cancer cells in the blood stream actually reached bones of the extremities, but failed to survive because it was too cool for them there.

\* Given February 20 1940 before the Section on Medicine of The New York Academy of Medicine

With this idea in mind, namely, the possibly deterrent effect of cold on cancer, he decided to make a clinical trial in the case of a woman with a far advanced carcinoma of the cervix. For months she had been taking several grains of morphine daily, in spite of which, her pain was so severe that she had been referred to Fay for chordotomy. It was decided to defer operation to see what the local application of cold to the fungating mass in the vault of the vagina might accomplish. Accordingly there was improvised a round metal container through which water was constantly circulated at a temperature between 40° and 50° F. Within 36 hours, pain had gone, and as time went on, the ulcerating mass began to diminish in size and, by the end of 5 or 6 weeks, had completely healed. Biopsies taken before and during the treatment showed, according to Lawrence Smith, that under cold, the carcinoma cells disintegrated, whereas, the normal connective tissue and normal blood vessels survived. The woman was temporarily restored to normal activity for several months, then developed a secondary brain metastasis, from which she eventually succumbed. Following this first cast of local application of cold, the method was applied to ulcerating cancers of the breast, cheek and skin. In all of these there was improvement locally, with recession in size of tumor and even healing of the ulcer.

After about 2 years experience with this local cooling treatment, Fay had the courage to initiate cooling of the body as a whole for a cancer located in regions not accessible to local cooling, for example, intractable pain from cancer involving the spine, pelvis, or abdomen. Here the patient was put to sleep by rectal administration of ivertin. This method of cooling the unconscious or semi-conscious patient from ten to eighteen degrees below normal for periods from a few hours to as long as 5 days is the so-called "Artificial Hibernation," "Frozen Sleep," or as we call it here, "Cryotherapy."

The patient receives chloral and bromides the night before, luminol the next morning. A Levine or Linhorn tube is passed into the stomach, then ivertin or evipal by rectum or intravenously renders the patient unconscious. He is now brought into an air-conditioned room, maintained at a temperature of 55° F., is laid naked on a bed, the thermocouple is inserted into the rectum, a rubber-covered wire cable leads from the patient's rectum to the recording dial on the wall. Wrists and ankles are tethered with padded restraining loops. The patient's

trunk, from shoulders to half way down the thighs, is now packed in loose ice, the fragments of which are not larger than those of nut coil. The ice pack is maintained until the rectal temperature reaches 90° F. This usually takes from 1½ to 2½ hours, in one very obese patient as long as 20 hours. When 90° or 91° by rectum has been reached, the ice is removed, the patient dried, and at a room temperature of 55° F., the patient's rectal temperature goes down to the 80's.

Should the temperature become too low, blankets and lukewarm hot water bags surround the patient. Should the temperature begin to rise, ice bags without cloth coverings are applied to the trunk and upper thighs. Temperature, pulse, respiration and blood pressure are charted every half hour. A telephone in the room enables the nurse to call resident physicians at any time should the patient's general condition, color, respiration, or pulse show any marked changes.

Through the stomach tube, 2 ounces of normal saline with 10 per cent glucose are instilled every hour. For restlessness, sodium amytal or sodium luminal or even seconal are given in suitable quantities. The 20 per cent paraldehyde in gum acacia, originally used, was abandoned as too irritating to the gastrointestinal tract. Twice a day the stomach is siphoned empty, and once a day the stomach is lavaged with a quart of normal saline, one pint at a time.

When it is time for discontinuing treatment, the air-conditioning apparatus is shut off and the room is allowed to come up to normal room temperature. The patient is covered with blankets and the body temperature slowly rises to normal. This usually takes 6 to 8 hours. The patient is not returned to the ward until normal temperature is reached. Experience has shown that nurses must be warmly dressed to care for these patients in a room at 55° F. The nurse is on for a period of 4 hours, then is relieved by another, and returns again after 4 hours to complete the second half of her 8 hour tour.

Selection of cases and conduct of this clinical investigation were assigned to a committee on which were representatives of surgery, general medicine, gynecology, pathology and physical therapy. Only cases of microscopically proven malignancy, inoperable and radioreistant were considered (140 applications, 26 acceptances).

Patients considered suitable for acceptance were those still up and about or in fair general condition, if bedridden (carcinoma of bladder, for example), with intractable pain or large, measurable tumor masses.

## GROUNDS FOR REJECTION\*

- 1) Bed ridden patients, as a rule are too weak and with too brief an expectancy of life
- 2) Patients with marked anemia (Hb 60 per cent or less), as likely to develop necrosis of uvula, or of mucous membrane of cheeks
- 3) Patients with carcinoma of stomach, as unlikely to absorb fluids and sedatives effectively
- 4) Patients with lung metastases Their presence, demonstrated by x-ray, increased the hazard of pneumonia A few scattered metastases did not indicate rejection, but lungs riddled with metastases or a chest full of fluid precluded acceptance
- 5) Patients with pathological fracture of the femur The markedly reduced peripheral circulation while under general cryotherapy made the use of fixation by splints or casts hazardous The unconscious patient's position must be changed from time to time to avoid the possibility of decubitus

*Conditions treated to date*

Carcinoma	22	Melanoma	1
Sarcoma (neurogenic)	1	Leukemia (acute)	2
Drug addiction	1		

*Locations of Carcinoma (primary)*

Prostate	2	Rectum	2
Breast	6	Thyroid	1
Colon	2	Urinary bladder	3
Uterus	3	Liver	1
Ovary	2		

In addition to malignancies it was appreciated that the effects of cooling might be tried out in many other fields, for example

- 1) Intractable pain from other causes than carcinoma or sarcoma
- 2) Tropical blood parasitic diseases resistant to commoner forms of therapy
- 3) Drug addictions

Incidental to relief of intractable pain from carcinoma it was found the patients had lost their craving for narcotics Consequently,

\* Formulated during this series and in part based on experience gained in observation of first patients

the method was tried by Fay and Smith on addicts with no cancer, with several apparently successful deprivation cures. At least the period of deprivation was passed by the unconscious patients who afterwards, for the time being, seemed to live without the drug without suffering discomfort.\*

- 4) Mental diseases, such as schizophrenia

#### CONCLUSIONS REGARDING GENERAL CRYMOTHERAPY

- 1) It was possible to reduce patients' temperatures from  $10^{\circ}$  to  $18^{\circ}$  F below normal for from a few hours to 3 days (Counting from time  $90^{\circ}$  F was reached on way down to time  $90^{\circ}$  F was reached on way out. Totalling 2,856 hours below  $90^{\circ}$  in 65 inductions on 26 patients)
- 2) Inductions can be repeated, at intervals, as many as five times or more depending on the patient's general condition
- 3) Risks from pneumonia and from nephritis seemed not as great as might be expected
- 4) In malignancies, striking relief from intractable pain with discontinuance of narcotics was noted in eleven of seventeen patients
- 5) Sooner or later pain returned, sometimes less severe, in others just as severe as before treatment
- 6) As time went on progressive cachexia was noted
- 7) Perhaps, if intervals between treatments were made shorter, a difference in recurrence of pain and progress of cachexia might be noted. This is to be given a trial, we have not had enough experience
- 8) Our material, available during the past four months, has not afforded sufficient experience regarding the effect of local refrigeration to justify drawing conclusions

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\* Details of the one case observed by us may be reported here. A woman of 46 had, for at least 15 years, been taking 6 to 8 grains of morphine daily. She was subjected to 4 days' crymotherapy at  $92^{\circ}$  F, then for 1 day more at  $98.6^{\circ}$  F, still under sedatives, 5 days in all, during which she stood the treatment well. Afterwards, for 2 days she was never left alone one moment. Since then for 8 weeks she has had no craving, and, for the first time in 7 years, menstruated normally a few days ago. It was interesting to note that, while under crymotherapy, gastric hypersecretion began at the end of the first 24 hours, amounting to between 1500-2500 cc in 24 hours and requiring intravenous replacement of fluids by 5 per cent glucose in normal saline. The gastric hypersecretion gradually subsided by the fifth day, when she was able to absorb fluids normally once more.

*Cardiovascular Aspects*

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Adjunct Physician, Cardiovascular Service Lenox Hill Hospital

The changes in the circulation caused by cooling the body are approximately what one would expect. After a preliminary rise, the rate of the pulse is decreased, but not in proportion to the temperature. It is unusual, even with the rectal temperature below 85° F., to observe a rate of less than 50 beats per minute. Irregularities are most often due to sinus arrhythmia or auricular fibrillation.

The blood pressure varies considerably. With short exposure of the patient to cold, it may show no significant change. During the "induction period" the systolic pressure, the diastolic pressure, or both may rise, or a typical epinephrin effect may be obtained, the diastolic pressure rising and the systolic falling. Quite consistently both show considerable decrease after long exposures. Often the blood pressure cannot be ascertained by the auscultatory method. Both arterial constriction and decreased arterial flow probably contribute in some measure to the difficulty of hearing Korotkoff's sounds.

The peripheral vascular tree undergoes profound constriction. Large arteries of the caliber of the dorsalis pedis, posterior tibial, or radial may be impalpable at low temperatures. Veins are often so constricted as to make simple venipuncture exceedingly difficult. A decreased body temperature is said to induce Raynaud's phenomenon even in normal individuals.<sup>1</sup> If Lewis and Pickering's<sup>2</sup> definition of Raynaud's phenomenon be accepted, namely, that the involved parts "become fully cyanotic or waxy," it may then be stated that no example of digital artery spasm was observed either in the hands or feet of the patients.

Observations elsewhere<sup>3</sup> have shown that the circulation time in the peripheral vessels is prolonged when the temperature of the body is decreased. With the slowed pulse, low arterial pressure especially in the later stages, the obvious generalized vasoconstriction, and the slowed circulation time, it is plausible to assume that the cardiac output per minute is decreased. However, direct measurements of this variable are still to be made.

Electrocardiograms are interesting, but difficult to obtain because

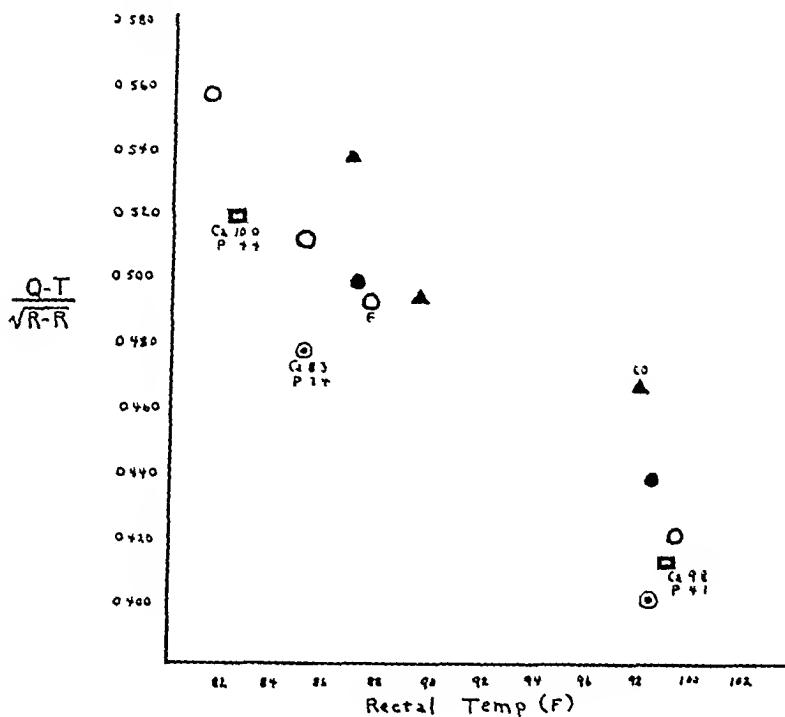


Chart 1

Chart 1—Twelve observations in 5 subjects (indicated by different symbols) on the relation of rectal temperature in Fahrenheit to the length of electrical systole expressed as Bazett's index ( $K = \text{electrical systole } / \sqrt{\text{cycle}}$ ) Ca, serum calcium, P, serum phosphorus, CO, a patient with myocardial infarction 18 months before, F, ventricular fibrillation. Two of the five patients were women. Their control values are within the normal range of  $K$ . The three men showed control values somewhat above the maximum normal, explainable in one on the basis of myocardial infarction.

of shivering. Wherever possible precordial Leads  $V_1$ ,  $V_3$ , and  $V_5$ <sup>4,5</sup> were recorded with an oscillograph type of instrument at half-normal sensitivity, in addition to the standard leads. In nine subjects the most constant change in the electrocardiogram was an alteration in the form of the final ventricular deflections, and a prolongation of electrical systole. The accompanying Chart I, which includes twelve observations on five subjects, reveals almost a linear, though inverse, relationship between temperature of the body and the length of electrical systole expressed as Bazett's index.<sup>6</sup> However, when the patient is warmed again, the Q-T interval does not return to normal for many hours and may not do so for several days (Fig. 1). Even when it does reach its control value, some abnormality of the T-wave, always present during crymotherapy, may persist for some time. Lengthening of elec-

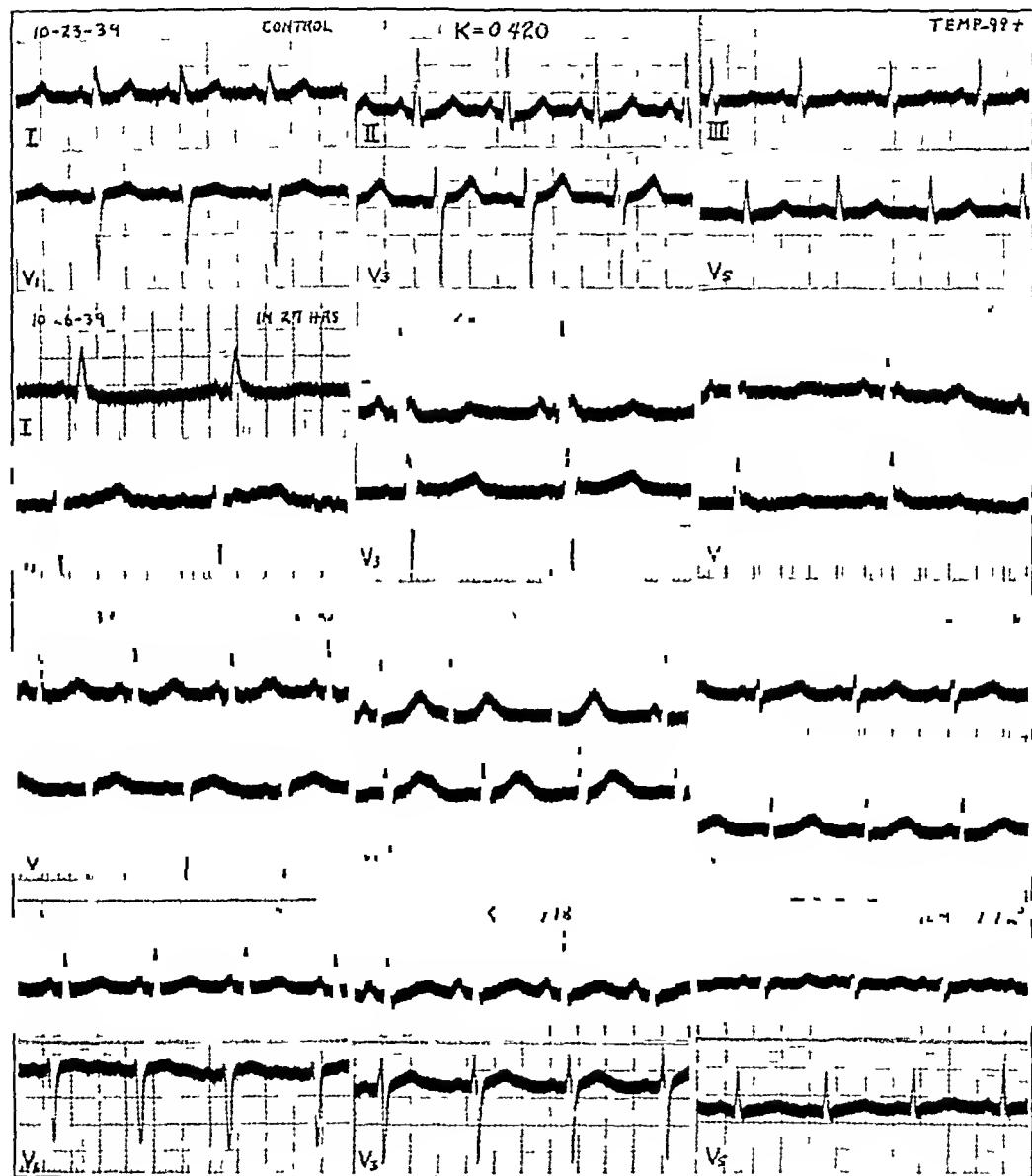


Figure 1

Figure 1—Standard electrocardiograms (I, II, III) at normal sensitivity of the string and precordial potentials ( $V_1$ ,  $V_3$ ,  $V_5$ ) at half-normal of case, D. L., age 39, carcinoma of the transverse colon with generalized metastases. The date of the recording, the rectal temperature at the time, and the systolic index, K, are recorded on each curve. "In 27 hours" means the time the patient's temperature was below  $98^{\circ} \text{ F}$ . "Out 6 hours" means the time after the patient's temperature had returned to levels above  $98^{\circ} \text{ F}$ .

trical systole was not accompanied by any significant change in the serum concentration of calcium or phosphorus<sup>7,8</sup> These facts suggest that the process responsible for prolonged electrical systole is a pathological one rather than a simple chemical retardation due to cold. Of interest was one patient who showed no prolongation of the Q-T interval during the therapy. She was receiving digitalis at the time, a drug known to shorten electrical systole<sup>9</sup>.

In four instances an unusual T-wave was encountered, usually recorded best in Lead II (Fig. 1, 10/26/39), but also seen in other leads. It was observed only when the temperature of the subject was below 84° F. This T-wave was characterized by a summit immediately after QRS, a return to the baseline, and a final summit smaller than the first. The precise significance of this unusual deflection is not known, but it is surmised that it may be the first evidence obtained in man in support of the dipolar nature of the regression process in cardiac muscle<sup>10</sup>.

The initial ventricular deflections did not reveal the same sensitivity to cold as the final ventricular deflections. However, there was sufficient effect (Fig. 1) on electrical excitation to cause slight widening of the QRS interval, and distinctive changes in the separate deflections. Similar remarks apply to the auricular wave.

Auricular fibrillation was observed in four of the nine subjects. This abnormal rhythm was encountered only when the temperature was above 85° F. In one subject it was abolished by a lower temperature.

No premature systoles were recorded while the subjects were abnormally cold. Soon after removal from the cryotherapy room, one subject showed a His-bundle premature systole followed by a temporary shift of the pacemaker to the His-bundle (Fig. 1, 10/27/39, Lead II).

#### SUMMARY

Decreased temperature of the body was observed to have the following effects on the circulation: the pulse rate is slowed, the blood pressure is variable but usually falls if an abnormally low temperature is maintained for more than 24 hours, there is marked generalized arterial, arteriolar, and venous constriction, abnormalities of the T-wave in the electrocardiogram are always present, and of the QRS group occasionally present, auricular fibrillation is common, electrical systole is prolonged, principally due to a delay of the recovery process, not related to changes in serum calcium.

*Hematology*

CARL REICH

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One control, a morphine addict, was treated for five days under cryotherapy. After the first day the hemoglobin and red blood count increased slightly. The total white count went up appreciably, with a rise in the percentage of polymorphonuclears, and a shift to the left. The sedimentation rate and platelets decreased. The cell volume went up. Toward the end of the treatment, the hemoglobin and red count dropped. The white count remained the same. There was a gradual return to a normal blood picture with discontinuance of the treatment.

In the carcinoma patients, a short treatment was associated with a rise of the hemoglobin and the red count. There was a marked increase of the white count and percentage of polymorphonuclears, with more immatures. The sedimentation rate and platelets decreased, and the cell volume increased. As for bone marrow from sternal puncture, the total nucleated cell count dropped. The percentage of granular elements increased, while the erythroid elements decreased. During the longer periods of treatment, the findings remained the same, except for a drop in the hemoglobin, red count and cell volume.

Two patients with leukemia were treated—one lymphatic and the other myeloblastic.

The lymphatic was in the last stages of the disease, and aleukemic. He showed no changes during treatment. The bone marrow was completely replaced by lymphoblasts, both by sternal puncture and at autopsy.

The acute myeloblastic patient was given two treatments of 12 hours each. The total white count dropped from 50,000 to about 10,000 during each treatment, and stayed down for a few days thereafter. The differential count of 95 per cent myeloblasts did not change, and the marrow was completely replaced by myeloblasts, during life and at autopsy.

*Blood Chemistry*

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In view of the small number of patients observed under cryotherapy and the absence of normal controls, no attempt is made to draw definite conclusions

This report presents the results of observations in eleven patients from whom blood was obtainable before, and 24, 48 and 64 hours under cryotherapy. The non-protein nitrogenous constituents of the blood, the plasma chlorides, the cholesterol partition, calcium and phosphorus, red cell volume, and sedimentation rate were studied in this group.

The non-protein nitrogenous constituents, before treatment was started, were within normal limits, with the exception of one patient in whom the urea nitrogen was elevated, the value being 27.7 mg. This patient showed an increased urea content of the blood after 24 hours under cryotherapy, the figure at this time being 38.5 mg. One other patient also showed a rise in blood urea from 8.8 to 17.8 mg. None of the other patients in this group revealed significant changes in any of the non-protein nitrogenous constituents.

The plasma chlorides were within normal limits before and during cryotherapy. The plasma protein changes were also without significance.

Changes in the serum calcium and phosphorus were not significant, while the serum cholesterol partition showed the percentage of free cholesterol to be rather constant before and during cryotherapy.

The red cell volume was increased under cryotherapy in four instances, the increase varying between 14 and 20 per cent.

The initial sedimentation rate was increased in all of the eleven patients under observation. Under cryotherapy there was a definite fall in the sedimentation rate, with the exception of three patients, in whom there was no change. However, it was noted that within 48 hours after cryotherapy, the sedimentation rate in those thus observed returned to about the pretreatment level.

*Basal Metabolism Determinations*

JACOB GEIGER

Assistant Chemist Lenox Hill Hospital

It has been shown by Rubner, Lusk and others that after short exposures to cold there is an increase in the basal metabolism rate as high as 180 per cent over the normal. This is ascribed to the mechanical and chemical mechanisms of heat regulation.

The effect of sedation and sleep have also been studied and it has been shown that the B M R may drop 15 per cent during sleep. Ordinary sedatives, in therapeutic doses, have little or no effect on metabolism. Patients undergoing cryotherapy present an opportunity of studying the effect of prolonged low body temperature on basal metabolism, possibly for the first time.

*Procedure* One or two days after admission to the hospital, a B M R determination was made under the usual conditions, i.e., after a night's rest and in the fasting state. Several control tests were made after administration of glucose and saline by mouth and after small doses of sedative, such as are now routine in cryotherapy. These controls showed no remarkable deviation from the normal. The next determinations were made at the end of 24 hours of body temperature below 86° F., 48 hours, and in one case, 72 hours. Several patients were rechecked 24 hours after their return to the wards.

The results here presented were obtained on patients who were fairly quiet and cooperative. They were told that a breathing test was about to be done, and were asked to breathe slowly and quietly, which they did surprisingly well. There was, in some patients, moderate muscular twitching, but if this was at all marked, or restlessness increased, the test was discontinued. One nurse held the lips in place over the mouthpiece, another held the nosepiece in place, while we watched continuously for leakage and other factors which might give an erroneous result. Some patients could be tested at the end of 24 hours but were too restless at the end of 48 hours. The body temperature ranged from 85.5° to 86.2° F. There was a rise in two cases of from  $\frac{1}{2}$  to 1° F. during the test.

*Results* Thirteen patients were tested. The highest B M R prelim-

inary to cryotherapy was +39 per cent, the lowest, -12 per cent. Ten tests were run at the end of 24 hours. Of these, three showed an increase of 3 per cent over the preliminary B M R, and seven showed a drop of 2, 2, 10, 13, 17, 18 and 25 respectively.

Six tests were run at the end of 48 hours, one showing a rise of 14 per cent, and five showing a decrease of 10, 10, 17, 32 and 50 over the preliminary B M R.

One test run at the end of 72 hours showed a drop of 22 per cent. One patient, a drug addict, undergoing withdrawal treatment, was tested at the end of 24 hours. The B M R was +17 per cent. Three patients tested after return to the wards, showed a B M R about the same as the preliminary.

*Tentative Conclusion* It would seem, from this small series, that in patients undergoing cryotherapy, there is a definite drop in the B M R at the end of 24 hours and a further drop at the end of 48 and 72 hour periods. Since short exposures to cold have been shown to increase the B M R noticeably, it may be concluded that metabolism is depressed by continued low body temperature.

### *Neurological Observations*

THOMAS K. DAVIS

Neurologist Lenox Hill Hospital

For various reasons my report is not based upon all the patients who have received cryotherapy. On eight patients I have done complete neurological examinations before and after the treatment and during the treatment have carried out as much of a neurological examination as is possible on a semicomatose patient.

In no instance were there any neurological findings after the treatment differing from the neurological status before. However, during the treatment there was in all cases a disappearance of the pupillary light reflex. In those patients in whom I have been able to observe the fundi, the fundi were normal, as one would expect.

In two instances, during the treatment, while the various deep reflexes were slightly if at all stronger than before, there were crossed tibial reflexes not previously observed. (These were absent following

the treatment) Also in one patient in the treatment, a nil response to plantar stimulation was obtained Both before and following treatment, this patient's plantar reflexes were normal

This transient change of plantar response in one patient and the transient crossed reflexes in two other patients suggest that when the body temperature is reduced there is a tendency for the pyramidal tracts to lose part of their normal control One finds that the coldness of the extremities tends to produce a pseudospasticity which is probably local This being so, it is not easy to be dogmatic regarding the reflexes, but as I said before, the occasional appearance of crossed reflexes would seem to lie outside the province of the local status and may concern the temporary functioning of pyramidal tracts

In one patient a hyperesthesia of the left side of the face, possibly occasioned by a metastasis, which was present before the treatment, was unchanged after the treatment

On the mental side, during the treatment the patients were at times restless and uneasy Although only semiconscious, they did in some instances resent the wrist restraints or ask to be covered It was possible to get slightly in touch with the patient One gave the name of the President when asked and added "9 and 7" correctly, but the same patient did not respond when asked to give the name of the hospital After the treatment this patient had no memory of anything which had happened Another patient, though semicomatose, opened her eyes on command She seemed to understand a question regarding how she felt and replied "good", afterward she had no memory for any part of the period

Another patient even remarked—"Am I being a good guinea-pig?" Also she asked if treatment was being given her for a longer period than time But this patient did not recall these things afterward

Another patient appeared to understand simple questions but mumbled the same perseverated replies to all questions Also she had complete amnesia for this afterward

I am not inclined to speculate on the factors involved in this kind of transient accessibility Its transient character reminds one of the semicomma seen in epidemic encephalitis One wonders whether the reduced temperature is the factor which works to produce the complete amnesia afterward I doubt if the sedation employed alone explains the amnesia

In retrospect, none of the patients have looked upon the treatment as unpleasant

*Temperature Observations*

MADGE C L McGUINNESS

Director of Physical Therapy, Lenox Hill Hospital

The usual skin temperatures observed in this study are entirely relative, since we have not the required constant-temperature room for this purpose, and in the cryotherapy room our semi-conscious patients cannot cooperate as well as the usual subject studied

Observations on two men and one woman are shown Joseph M (M 1), Age 41, with cancer of the rectum, the most nervous of the twenty-seven patients, is alternately apprehensive and euphoric (Chart 2)

James M (M 11), Age 47, with lower gastrointestinal carcinoma, less nervous than M 1 ordinarily, but extremely restless and spastic in the cryotherapy room (Chart 3)

Mrs C (F 5), Age 37, with cancer of the left ovary, most cooperative and docile of all the patients, who was in a state of tonus apparently both in and out of the cryotherapy room as evidenced by her reduced oscillometric readings (Chart 4)

In the cryotherapy room, constant sedation and hourly feedings of glucose in saline had a distinct bearing on the temperatures. Most important was the almost constant shivering and, despite restraining cuffs and anklets, the tendency to move continuously

In the cryotherapy room the temperature varied, being 55°F at the wall where the recording thermometer wrote its story, 60°F at the opposite wall near the window, 59°F at 12 inches from the knee, from 64° to 66°F on the bed between the calves and, on the Dakin pad covering the crotch, 71°F, rising or falling as the rectal temperature varied

The units used were the U M A and the Leeds-Northrop recording temperature thermocouple specially made for this work. As Dubois<sup>1</sup> and Hardy<sup>2</sup> contend, each piece of work is unique as it involves so many variables, beginning with the air temperature of room or thermocouple and ending with the personal equation, running the gamut in between, of patient and worker cooperation, liquid intake, changes in rectal and room temperature, exercise, shivering and general condition of patient

### Chart 2—COMPARISON OF SKIN TEMPERATURES

Mr M 1	Age 41	Ca. Rectum (Intestinal Fistula)					
Room Temperature	78	° F					
Thermocouple	74 5	55 Head Wall					
Between Calves	78 80	60					
Rectal		59 60					
Mouth	99 2	87 75					
B M R —12	Wgt 136	Wgt —122					
B P 130		B P 118 — 100					
90		80 70					
Great Toe	R 84	60 25					
	L 85	62 25					
Ball	R 85	62 50					
	L 85	63 75					
Heel	R 84	63 25					
	L 86 5	63 75					
Ankle	R 87 2	63 75					
	L 85 75	69 25					
Calf	R 87 75	66 25					
	L 85 75	67 50					
Knee	R 88	68					
	L 86 25	72					
Thigh	R 89 75	78					
	L 89 25	81 5 Urine 82 ( ) Rectal 87 4					
Oscillometric Readings							
Right	Ankle 3 00	Calf 4 25	Thigh 2 50	Ankle faint	Calf 0 25	Thigh 0 50	spastic
Left	2 50	3 25	2 25	faint	0 25	0 50	shivering

### Chart 3—COMPARISON OF SKIN TEMPERATURES

Mr M 11	Age 47	Ca. Lower Intestine	Wgt 138 (was 185)	
Room Temp	71	° F	° F	
Thermocouple	72	55 Head Wall	60 Foot Wall	
Rectal	98 2	60		
Between Calves	74	64		
B M R —13		B P 130 — 90	lowest	
B P 116 — 102	90 78	88 50		
Great toe	R 79	67		
	L 77 75	68 25		
Ball	R 80 75	66		
	L 79 25	64		
Heel	R 82 25	66		
	L 80	64 25		
Ankle	R 83 25	67		
	L 81 75	66		
Calf	R 85	72		
	L 85	72		
Knee	R 90 25	71 75		
	L 89 50	74 25		
Thigh	R 91 5	75 75		
	L 89 75	79 = Chill 78 quieter		
Breast	R 89 to 90 75	72 to 73 75		
	L 89 75 to 90 50	71 to 72 Urine 84 Rectal T 86 9		
Oscillometric Readings				
Right	Ankle 1 75	Calf 2 75	Thigh 3 50	Unable to take readings—Constant shivering spasticity continuous movement
Left	1 25	2 00	3 50	

### Chart 4—COMPARISON OF SKIN TEMPERATURES

Mrs C	Age 37	Ca. Left Ovary	Wgt 105
Room Temperature	71	° F	° F
Thermocouple	70	54 Head Wall	60 Foot Wall
Between calves	76 5	60	
Rectal 10 minutes	100 7	59	
Vaginal 10 minutes	100 8	88	
B M R + 14			
Great toe	R 70 5	61 5	Spastic
	L 72	62 25	Lett arm markedly
Ball	R 75 25	64	adducted
	L 72 25	64 25	Marked tonus
Heel	R 77 25	64	
	L 75 25	67 25	
Ankle	R 82	65	
	L 81 5	66 75	
Calf	R 84 75	69	
	L 86 75	69	
Knee	R 87	67 25	
	L 87 25	Ice applied	
Thigh	R 87 25	Rectal T rose	
	L 87 75	from 80 to 87 + 5	
Oscillometric Readings			
Right	Ankle 0 5	Calf 1 50	Thigh 1 75
Left	0 5	1 25	1 75
	Ankle faint	Calf 0 25	Thigh 1 00
		0 5	

When the patient was especially active, moving the right arm and hand continuously, trying to take off the ice bags or attempting to cover himself, the temperature varied on either side, from tenths to 3 or more degrees Fahrenheit. This is shown in the chart of M 11 who was never still for one moment and shivered continuously. Drugs seemed to have very little effect upon this patient.

Oscillometric readings were taken in the cryotherapy room when possible and showed marked variations and decreases in oscillations, with shallow and deep breathing, chills, exercise and spasticity.

The range of error was constant for the devices used. Between 90° and 110°F, the degree of error was plus or minus 1. When the temperature was below 90°F, the degree of error was plus or minus 1.25. This range has been established by the U. S. Bureau of Standards.

*Conclusions* Different parts of the body cool to varying degrees. Shivering and movement increase temperature.

Greater changes occur from a higher temperature of 78°F than from 71°. Vasoconstriction is marked, thus decreasing the conductivity of skin, so that the blood is held within the body. Further studies are required to properly evaluate varied findings in temperatures at other levels than those shown.

### *Urologic Aspects*

HERBERT R. KENYON

Urologist, Lenox Hill Hospital

There were eight patients with involvement of the urogenital tract, falling into three groups:

- 1 Primary neoplasms
- 2 Secondary invasion of the urinary tract
- 3 Extra-urinary tumors producing obstruction

Group 1 includes two cases of prostatic carcinoma and three primary vesical neoplasms. The first patient with carcinoma of the prostate also had widespread skeletal metastases with pathologic fracture of a rib. His response to radiotherapy was poor and his pain uninfluenced by large doses of opiates. Although his condition was precarious, he re-

ceived one treatment at the urging of his physician which was followed by partial subsidence of pain. Unfortunately, he developed pneumonia on the third day after treatment and died four days afterward. The second patient has shown a more satisfactory response than any of the others. He was known to have a carcinoma of the prostate for nine months, during which time his condition had steadily deteriorated, the outstanding complaint being severe backache due to sacral metastases. This was resistant to x-ray therapy and alcohol injection of the sacral nerves. He had also developed a vesical calculus and lost 50 pounds within 6 months. It was impossible for him to lie on his back for more than a few minutes at a time. Transurethral resection and litholapaxy were performed, the tissue showing adenocarcinoma. After the first session in cryotherapy it was possible for him to lie comfortably on his back without the large doses of morphine and cobra venom that had previously been necessary. Although subsequent biopsies have shown no change in the structure of the tumor, and x-rays indicate further spread of the metastases, rectal palpation reveals a recession in the size and consistency of the primary tumor. Lately there has been a partial recurrence of pain, in a different location, for which additional treatment is now being administered.

Two of the patients with primary vesical neoplasm showed little benefit from treatment except for transitory diminution in the degree of pain. In both there were extensive recurrences following partial cystectomy and radiation therapy. One was complicated by a vesico-vaginal fistula with bony metastases, while the other presented extensive involvement of the inguinal and iliac nodes with edema of the legs. Both died within 3 months after receiving treatment without evidence that they had been favorably affected. The third patient had symptoms for 8 months and a papillary carcinoma had been observed 3 months before admission. It had resisted radiation and our admission cystoscopy disclosed a growth involving almost the entire right half of the bladder, including the sphincter and ureteral orifice, without demonstrable metastases. Following the first session of cryotherapy, sufficient relief was obtained to permit a considerable reduction in the dosage of narcotics. Further treatment resulted in definite betterment of both the symptoms and the general condition of the patient, despite the fact that later observations reveal no change in either the gross or histologic characteristics of the tumor.

in all of them Of the eighteen patients whose lungs were clear, only one developed pneumonia, which was a result of aspiration

Nose and throat cultures, routinely taken in all patients before treatment, were all negative for pneumococci and hemolytic streptococci Pneumococci were recovered and typed from the sputa of two of the pneumonias, while in the other three, no causative organism could be found

Although obviously this series is small, one gains the impression that the presence of pulmonary metastases may predispose to a complicating pneumonitis On the other hand there were eighteen patients whose lungs were clear clinically and by x-ray, who had a total of thirty-five periods of cryotherapy, with only one pneumonia

### *Roentgenological Observations*

FRANK HUBER

Associate Radiologist, Lenox Hill Hospital

X-rays of bone metastases (in two patients) taken at suitable intervals showed definite increase in size of previously noted defects, as time went on

### *Biopsies and Deaths*

RUDOLF M. PALTAUF

Pathologist, Lenox Hill Hospital

Of the twenty-two cases of carcinoma receiving general cryotherapy, only eight were followed up with subsequent histological examinations In five cases we were able to obtain from one to three biopsies during treatment and three of these were subsequently studied at autopsy In two cases, the study was limited to a comparison of material obtained before treatment and the postmortem examination One patient with malignant melanoma gave us the opportunity for histological study after one and after two treatments with cryotherapy

In all of these biopsy studies, the histological picture of the tumor, its cell characteristics and the appearance of the surrounding tissue appeared identical in every respect with that seen in examinations before the treatment.

Of the five cases representing our autopsy material, three cases were carcinoma of the breast, one carcinoma of the uterus and one carcinoma of the colon. In the carcinoma of the breast, the metastases were most widespread, including in one case the spleen. The three cases of carcinoma of the breast showed acute inflammatory lesions in the pancreas which varied in degree from focal areas of necrosis to hemorrhagic pancreatitis with extensive fat necrosis all along the surface of the pancreas and adjoining mesenteric and omental fat. This apparently was the immediate cause of death in one patient. In two other cases of carcinoma of the breast, marked necrosis of the tumor tissue was noted in all the metastases and in the absence of evidence of a terminal pneumonia or other complications, the cause of death in these patients must be attributed to cachexia and some chemical changes due to absorption of the toxic products from the necrotic tumor tissue.

In the case of carcinoma of the colon, metastases were found in the liver and ovary. In addition, a moderate degree of coronary sclerosis was noted. This patient developed an intestinal obstruction and an emergency cecostomy was performed without apparent relief, shortly before death occurred.

The last patient in this series died of a massive pulmonary embolus, the origin of which could not be demonstrated, but apparently came from the veins of the lower extremities.

The two other patients who came to autopsy after treatment with cryotherapy had leukemia, one myelogenous and one lymphatic. They gave the usual findings in such cases and marked pulmonary edema and congestion with infarction in one and pneumonia in the other.

We did not find any regression of the primary tumors or metastases, nor were we able to demonstrate unusual cell alterations or any changes which could be interpreted as effects of cryotherapy on the neoplastic tissue. Nothing characteristic or uniform was found, except perhaps the acute inflammatory lesions of the pancreas which occurred in three of the five cases of carcinoma.

Local cryotherapy was followed up by histological examination in one case, a proven carcinoma of the fundus uteri. Five days after the

curettage, a cooling canule was inserted in the uterus. Through this canule, which represented a long loop of tubing, water circulated. It entered at a temperature of 34° and returned at 50°, with an estimated temperature of 40-45° in the uterus. This patient was treated for 10 days with this local cold application and subsequently the uterus was extirpated. In comparing the histological appearance of the tumor in the curettement and in sections from the uterus, we found that while the tumor tissue in the curettement was well preserved and without much degeneration or necrosis, the tumor in the sections of the uterus showed a very marked, extensive and deep reaching necrosis. The uninvolved endocervix, although exposed to the same trauma of the cold-applicator, showed only slight erosion of the surface. Twenty-one days elapsed between the curettage and the hysterectomy. In reviewing slides from other cases of carcinoma of the uterus where similar or shorter periods elapsed between curettage and hysterectomy, we did not observe such changes. It cannot be definitely stated whether or not these changes were due to cryotherapy.

### *Clinical Manifestations*

*(General observations, pain relief, mortality, local cryotherapy)*

PAUL KURT SAUER

Associate Surgeon, Lenox Hill Hospital

Immediately following the application of ice there is a brief temporary rise of 1° to 15° F. As the effect of the evipal begins to wear off shivering becomes manifest and is most marked between 97° and 95°, then as the temperature goes down it diminishes. Usually temperatures were kept between 80° and 85° F. In two cases 79.6° F. was reached for less than 2 hours.

Basal metabolic rates and electrocardiograms cannot be accurately taken when shivering is pronounced.

There is coma vigil—the eyes must be instilled with castor oil and kept covered with vaseline gauze to prevent drying and possible corneal ulceration.

On the second and third days patients are quieter and less sedation is required

Catheterization is done every 12 hours

Upon emerging, often there is fever of  $100^{\circ}$ – $101.5^{\circ}$  F which may last for 1 or 2 days

There is more or less haziness of the sensorium for 24 to 48 hours after emergence

Pain is often complained of upon first regaining consciousness. It is often only during the second 24 hours that one may determine whether relief from pain has come to pass

Twenty-seven patients have been submitted to general cryotherapy. Twenty-two of these had carcinoma, one, melanoma, one, neurogenic sarcoma, two, acute leukemia, and one, drug addiction

Regarding relief from pain, the twenty-four cases of malignancy (22 carcinoma, 1 melanoma, and 1 neurogenic sarcoma) fall into three groups

First, a group of five with little or no pain, second, a group of eight with little or no relief of pain, third, a group of eleven with marked relief of pain

In five patients of the second group, relief occurred for very brief periods

1 A patient with carcinoma of the bladder with extensions to the vagina and the rectum. Pain only at urination. This was relieved for about 48 hours after the first induction, but recurred, and was not alleviated by subsequent inductions

2 A patient with carcinoma of the breast with metastases and a healed pathological fracture of the femur, there was relief for about 24 hours

3 A patient with carcinoma of the uterus with pelvic metastases was not relieved of her original pain in the left leg but was found, subsequently, to have an obstructed ureter. The obstruction was relieved and her pain subsided

4 A patient with a neurogenic pelvic sarcoma experienced about 75 per cent relief for a period of only 36 hours after the first induction, then pain returned with original severity, and was not affected by a subsequent 3-day induction

5 A patient with carcinoma of the breast with wide spread metastases was relieved for 72 hours

Three other patients in this group experienced no relief of pain

In the third group, prior to induction, all of the patients had been taking varying quantities of sedatives Many of them required the administration of morphine over a period of months, and at times as much as 4 grains per day Following the induction these same patients required no sedation, and even those who had had large doses of morphine over a period of months were comfortable and apparently had no desire for morphine This relief varied in quality and length of time

Eventually recurrence of pain occurred in all cases In some, as early as 24 hours after cessation of treatment, and in one case the relief lasted as long as 8 weeks In some, the recurrent pain was not as severe as originally, consequently these patients required less sedatives, in others, the pain on recurrence was just as severe as before treatment

Pain recurred at sites other than originally noted in 3 cases In one, a sciatic pain replaced the original sacrolumbar pain, but even then the patient was able to sleep on his back, which he had not been able to do for a year previous to his first induction Incidentally, this was our first case, and his one question two days after emerging was, "When can I have another treatment?" In another, pain in the left hip replaced a pain in the cervical spine In the third, severe abdominal pain was abolished, but pain recurrence manifested itself in the chest

As a rule, visible and palpable subcutaneous metastases did not diminish or soften after general cryotherapy However, two exceptions are worthy of note

One was a patient with carcinoma of the thyroid with a tracheotomy One week after her first induction it was noted that a nodule of the right lobe of the thyroid about the size of a walnut had disappeared, the carcinomatous granulations surrounding the tracheotomy wound had disappeared and new epithelium was beginning to grow from the edges of the wound

The other patient had a carcinoma of the transverse colon, previously resected, with metastases to the liver, which was palpable four fingers' breadth below the costal margin and was stony hard After the second induction, the liver's size had regressed so that it was barely palpable and felt considerably softer Eight weeks later, however, the liver had again regained its original size and hardness This patient had relief from abdominal discomfort for at least 12 weeks, but pain recurred in his chest, which was filled with pleural metastases, and was not relieved

His general condition precluded further inductions

Metastatic nodules in a breast scar and on the back of one patient were noted to have increased in size despite three general inductions

Out of 27 patients inducted, 13 have died subsequently. The causes of death and the length of time after their last induction are as follows

1	E	Carcinoma of prostate Pneumonia	6 days
2	S	Carcinoma of bladder Pulmonary embolism	22 days
3	H	Carcinoma of breast Cachexia, pancreatitis	31 days
4	R	Carcinoma of cervix Cachexia	44 days
5	K	Carcinoma of thyroid Suicide	22 days
6	B	Carcinoma of breast Cachexia, pancreatitis, shock	In room at end of induction with rectal temperature 97.5°F
7	V	Neurogenic sarcoma Postoperative (N Y Hosp.)	22 days
8	G	Carcinoma of bladder Cachexia	46 days
9	O'C	Carcinoma of colon Obstruction, postoperative	2 days
10	A	Leukemia	1 day
11	T	Leukemia Cerebral hemorrhage	8 days
12	H	Carcinoma of breast Pancreatitis	6 days
13	K	Carcinoma of bladder Uremia	31 days

In two cases of acute leukemia—one lymphatic and the other myeloblastic—the course of the disease was not affected. We have had no experience with chronic leukemias.

## LOCAL CRYMOTHERAPY

Local crymotherapy implies local cooling of accessible malignant tumors. This is accomplished by means of suitable coils of rubber or metal tubing, or hollow metal containers of special conformation, applied to the tumor's surface, through which ice water ( $40^{\circ}$ - $50^{\circ}$ F) is kept circulating for 23 out of every 24 hours.

Two patients received local crymotherapy. One had carcinoma of the fundus uterus which received local crymotherapy for ten days before subsequent hysterectomy. The histological findings are reported by Dr. Paltauf elsewhere in this report. The other had metastatic carcinoma of the cervical nodes following an excision for carcinoma of the lip some years previously. At the time of admission the left side of his neck was stiff and indurated. Motions of the head and of the left arm were so painful that even reading a newspaper occasioned extreme discomfort. Within 24 hours after the local application of ice water coils, he himself called attention to the softening of the neck tissues and was able to use his left arm without pain. A week later the induration of the left side of the neck had diminished so that discrete glands were palpable. After two weeks, the mass in the neck had diminished to a size about 2 by 2 inches. He left the hospital soon after this and died at home 2 weeks later from a carcinomatous obstruction of the sigmoid and peritonitis.

## CONCLUSIONS

- 1 In eleven out of seventeen cases of intractable pain due to carcinoma, there was sufficient alleviation of pain to obviate the necessity for the administration of narcotics for variable periods of time.
- 2 No significant histological changes at autopsy in the appearance of carcinomata treated by *general* crymotherapy have been observed.
- 3 Our experience with *local* crymotherapy is too limited to warrant comment.
- 4 Investigation of this method should be continued, not necessarily limited to carcinoma. Investigation might be made as to its applicability in such other diseases as Hodgkin's disease, lymphogranuloma venereum, subacute bacterial endocarditis, drug addictions, blood dyscrasias, and tropical blood-parasitic diseases of an intractable nature.

*Discussion*

W LAURENCE WHITTEMORE

Physician City Hospital

Aside from Doctors Fay and Smith's report in August 1939 there is no reference to cryotherapy in the *Index Medicus*, and one may say that in New York our general knowledge of this procedure is based on the work carried on so ably in Lenox Hill Hospital and reported on so fully in this report

It is learned that local tissues may be cooled down to  $40^{\circ}$ - $50^{\circ}$  F without harm, and general hibernation demonstrates the fact that man's temperature can be cooled down  $10^{\circ}$ - $18^{\circ}$  F for a period of 3 days duration

In Philadelphia one patient was subjected to this treatment for 8 days

A T Rasmussen<sup>1</sup> reported that Mares and Hillich in 1889 reduced the temperature in an hysterical woman to  $92.50$  Fahr

Beginning with Buffon in 1749 many of these early experimenters have pointed out that exposure to cold alone will not produce true hibernation, but often a torpid condition that is entirely and physiologically different from true hibernation

Marshall Hall<sup>2</sup> in 1831 demonstrated this when he found that after destroying the brain and spinal marrow in a truly hibernating hedgehog, the heart continued to beat for 10 hours Cushing and Goetsch<sup>3</sup> in 1915 successfully demonstrated the same experiments on animals

Marshall Hall 100 years ago also drew attention to the fact that hibernating animals were easily disturbed by noises and touch This has been repeated so often that one might be forgiven for suggesting that all unnecessary disturbances and noises be kept minimal in the cryotherapy room Observations might be made whether or not in induction some patients leaned more towards cold torpor, and others towards true hibernation

One may wonder if there is not a link between the successful demonstration of regression of cancer tissue at  $40^{\circ}$  to  $50^{\circ}$  F and that of general hibernation at  $79^{\circ}$  F Possibly with further study of general hibernation this latter figure may be considerably lowered

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## PROCEEDINGS OF ACADEMY MEETINGS

## STAFFED MEETINGS

MARCH 7—*The New York Academy of Medicine* Executive Session—a] Reading of the minutes ¶ Papers of the evening—Clinical manifestations and management of disturbances in water metabolism—a] Medical considerations, Daniel W. Atchley, Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University, b] Surgical considerations, Frederick A. Coller, Professor of Surgery, University of Michigan, Discussion, John P. Peters, New Haven, William F. MacFee ¶ Report on Election of Members

MARCH 21—*The Harvey Society* (in affiliation with *The New York Academy of Medicine*) The Sixth Harvey Lecture, "Utilization of Selective Microbial Agents in the Study of Biological Problems," René J. Dubos, Associate Member, The Rockefeller Institute for Medical Research

## SECTION MEETINGS

MARCH 5—*Section of Dermatology and Syphilology* Presentation of cases—a] Skin & Cancer Unit of Post-Graduate Medical School, Columbia University, b] Miscellaneous Cases ¶ General Discussion ¶ Executive session

*Section of Surgery*—The Section of Surgery held no meeting on its regular date but instead met with the Section of Medicine on March 19

MARCH 12—*Combined meeting Section of Neurology and Psychiatry and the New York Neurological Society* Presentation of cases—a] Recovery in amyotrophic lateral sclerosis treated with tocopherol (vitamin E), presentation of two cases, I. S. Wechsler, b] Supratentorial hemangioma with hemorrhage,

presentation of two cases, Iri Cohen ¶ Discussion—Joseph L. J. King, Joseph Globus ¶ Papers of the evening—a] Spinal epidural infections, surgical and pathological consideration, Jefferson Browder ¶ Discussion—Harold R. Mervirth, Iri Cohen, b] Focal cerebral ischemia and reactive gliosis following experimental vascular spasm, Francis A. Lehlén (by invitation) ¶ Discussion—Harold G. Wolff, Lewis Stevenson ¶ Executive session

MARCH 13—*Section of Historical and Cultural Medicine* Reading of the minutes ¶ Papers of the evening—a] Jean Niccolis Corvisart, Physician to the Emperor Napoleon, Paul E. Bechet, b] An American Precursor of Freud, A. A. Brill ¶ Discussion—Clarence P. Oberndorf ¶ General discussion ¶ Executive session, Report of Nominating Committee

MARCH 14—*Section of Pediatrics* Reading of the minutes ¶ Papers of the evening—a] Observations on jaundice in childhood and in the newborn, Samuel B. Weiner (by invitation), Miriam Reiner (by invitation) ¶ Discussion by Harry Sobotka, Bela Schick, b] The allergy concept of the hypertonic state, Miner C. Hill ¶ Discussion by Sidney Haas, Louis A. Van Kleeck (by invitation), c] Diagnosis and treatment of coxa plana and epiphysiolysis, Beckett Howorth, d] Serum sickness and inaphylaxis in 6211 cases treated with different kinds of horse serum, Ferdinand Kojis (by invitation) ¶ General discussion ¶ Executive session

MARCH 15—*Section of Orthopedic Surgery* Executive session—a] Reading of the minutes, b] Appointment of nominating committee ¶ Presentation of cases—a] Mobile knee after synostosis, Lewis Clark Wigner ¶ Papers of the evening—a] Treatment of ununited fractures

of the neck of the femur—subtrochanteric osteotomy, James S Speed, Memphis (by invitation) ¶ Discussion—Samuel Kleinberg, b] Present methods of treatment of cerebral palsy, Winthrop M Phelps, Baltimore (by invitation) ¶ Discussion—Arthur Krida ¶ General discussion

MARCH 18—*Section of Ophthalmology*—Instruction hour—Evaluation of present methods of refraction, Benjamin Friedman, Demonstration—Instruments used in the diagnosis and correction of reading disability ¶ Executive session—a] Reading of the minutes, b] Appointment of nominating committee ¶ Papers of the evening—a] Reading retardation a problem to be solved cooperatively, Stella S Center Litt D, Director, Reading Clinic, N Y University (by invitation), b] Reading disability from a neurological viewpoint, Earl C Cheshire (by invitation), c] The effect of vision on reading disability, Brittain F Prine ¶ Discussion—Conrad Berens ¶ General discussion

MARCH 19—*Combined Meeting Section of Surgery and the Section of Medicine* Executive session—a] Reading of the minutes, b] Appointment of nominating committee for each Section ¶ Papers of the evening—a] Mechanism and medical management of chronic ulcerative colitis, Thomas T Mackie, Moore A Mills (by invitation, b] Surgical treatment of chronic ulcerative colitis, Henry W Cave ¶ Discussion—Burrill Crohn, John H Garlock ¶ General discussion

MARCH 20—*Section of Genito-Urinary Surgery* Executive session—a] Reading of the minutes, b] Appointment of nominating committee ¶ Papers of the evening—Symposium on prostatectomy—1] A suggested new type of anesthesia for prosthetic surgery, John A Taylor, b] Transurethral management of prostatic disease in patients over 75 years of age (motion picture), Alf H Gunderson, LaCrosse, Wis (by invitation), c] Su-

prapubic prostatectomy, its differential indications and limitations, modifications in technique (motion picture), Cliford W Losh, Des Moines, Ia (by invitation), d] Perineal prostatectomy, 1] statistical survey, indications and technique (motion picture), J A Campbell Colston, Baltimore (by invitation) ¶ General discussion — Nathaniel P Rithbun, George F Hoch

MARCH 20—*Combined Meeting Sections of Otolaryngology of The New York Academy of Medicine and the Philadelphia College of Physicians* Before the meeting there was a demonstration in the anteroom of postoperative results ¶ Executive session—Section of Otolaryngology of the Academy—a] Reading of the minutes, b] Appointment of nominating committee ¶ Paper of the evening—Endaural fenestration of the horizontal semicircular canal for otosclerosis Indications, technique, observations as to early and late postoperative results, Julius Lempert (by invitation) ¶ Discussion—Edward Campbell, Philadelphia (by invitation), George Shambaugh, Jr, Chicago, (by invitation), Joseph Sullivan, Toronto, (by invitation) William Greenfield, Hackensack (by invitation)

MARCH 26—*Section of Obstetrics and Gynecology* Executive Session—a] Reading of the minutes, b] Appointment of nominating committee ¶ "Asphyxia Neonatorum" (moving pictures), Henry Rascoff (by invitation) ¶ From the Gynecological Service, Harlem Hospital —1] Presentation of cases—Abdominal pregnancy with unusual complication, Elias Rauch (by invitation), b] Papers of the evening—1] Differential sign between giant ovarian cysts and ascites (lantern slides), George Blinich (by invitation), 2] A simple method of therapeutic abortion combined with sterilization (lantern slides), Avraam Shukuris (by invitation), 3] Photography of the cervix, Henry C Falk

BULLETIN OF  
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OF MEDICINE



JUNE 1940

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ADRENAL INSUFFICIENCY<sup>1</sup>\*

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CLINICAL PICTURE

**A**DRENAL cortical insufficiency in man, as represented by Addison's disease, may develop at any age although it occurs most frequently between the ages of 20 and 50 years. It is characterized in most cases by the insidious development and progression of asthenia and fatigability although not infrequently adrenal crises may give the first evidence of the disease. The symptoms are usually accompanied by the appearance of brownish pigmentation which increases over a period of months and which may be blotchy in its distribution or generalized. It is most intense on the knees, nipples or in the axillary folds as well as on the exposed parts, particularly the knuckles. The most characteristic feature of the pigmentation is the appearance of small brown or gray-black patches on the lips, gums, tongue or cheeks. In some cases, pigmentation may be entirely absent while in others it may exist in combination with numerous areas of depigmentation (Figs. 1 and 2).

Gastrointestinal symptoms are usually present and occasionally dom-

\* Delivered October 27, 1939 at the Twelfth Graduate Fortnight of The New York Academy of Medicine.  
• Many of the studies presented were made in collaboration with Drs. D. W. Atchley, J. Stahl, J. W. Ferrebee and C. V. Rasan Jr.



Fig 1—The presence of both pigmentation and depigmentation in a patient with Addison's disease



Fig 2—Depigmentation associated with profound pigmentation in another Addisonian patient

inate the disease picture. The appetite is almost invariably capricious and periods of anorexia occur with great regularity. This latter symptom is associated with infrequent bouts of vomiting which usually take place in the morning. During crises, emesis increases, there may be "coffee-ground" vomitus and finally there may be complete gastric intolerance. Abdominal pain is often present and may suggest disease of the biliary tract or even peptic ulcer. Diarrhea is only an occasional complaint.

Hypotension is almost always present in Addisonian patients whose symptoms are sufficiently marked to cause them to seek medical aid. The systolic pressure is usually less than 100 mm Hg but it may and frequently does rise during excitement to higher levels for short periods of time. During severe crises, the systolic pressure may fall to 50 mm Hg or even less and the pulse pressure is often only 10 mm Hg. The pulse is characteristically small in volume although it is occasionally full and soft. Under the influence of pain or emotional stress the pressure, even during crises, may momentarily rise to normal levels.

In a few instances hypoglycemia, with the symptoms and signs which characterize that state, dominates the clinical picture in Addison's disease. In most cases hypoglycemic episodes appear relatively late in the disease, particularly among patients already under treatment with salt.

The adrenal crisis consists of an abrupt increase in the intensity of the disease manifestations, notably weakness, prostration, hypotension, gastrointestinal symptoms and transient neurological disorders which may include confusional states as well as abnormal reflexes. In the course of a few hours or a few days, either spontaneously or as a result of an acute infection, or because of a surgical procedure, a severe emotional upset or the withdrawal of salt from the diet, the tempo of the disease process accelerates with alarming rapidity. The patient frequently dies during the crisis if energetic therapy is not instituted promptly, and occasionally dies despite the best possible treatment. The terminal crisis is often associated with a rise of temperature to 104 or 105° for which no adequate explanation may be found.

#### DISTURBANCES IN PHYSIOLOGY

Thomas Addison, in 1855, pointed out for the first time that "universal disease of the capsules" is incompatible with life and stated that

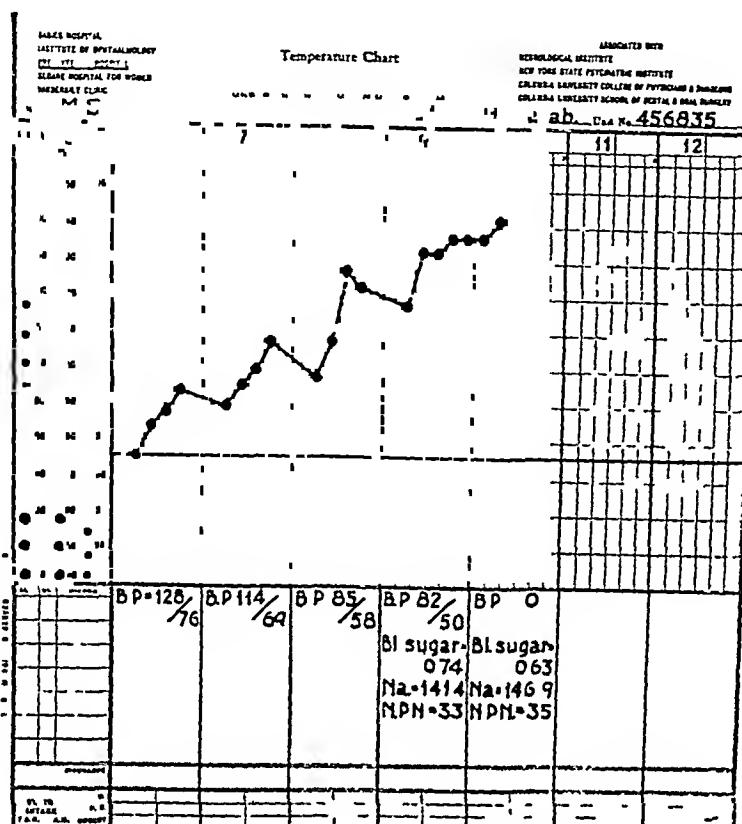


Fig 3.—Typical fatal terminal rise in temperature without adequate explanation at autopsy

aside from this observation the function of these structures "is almost, or altogether, unknown" At the same time, Addison predicted that the further study of disease of the adrenal glands might lead to some understanding of their physiological activity This prophecy has in recent years been amply fulfilled and it is to a consideration of problems of the functions of the cortex of the adrenal glands and the treatment of adrenal insufficiency that I should like to call your attention

#### SALT AND WATER METABOLISM

Among the most important disturbances resulting from insufficiency of the adrenal cortex are those related to electrolyte and water metabolism Baumann and Kurland<sup>1</sup> and Marine and Baumann<sup>2</sup> in 1927 demonstrated that the ablation of the adrenal glands in animals resulted in a decrease in the sodium concentration in the serum and an increase in

### SODIUM LOSS FOLLOWING ADRENALECTOMY IN DOGS

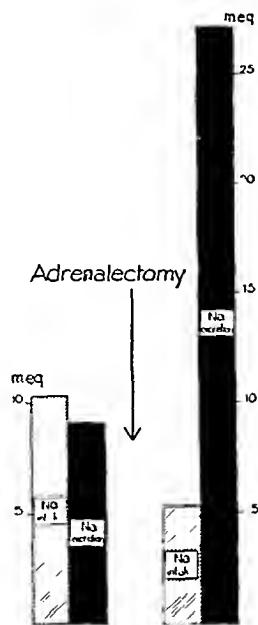


Fig 4.—Effect of adrenalectomy upon the urinary excretion of sodium in the dog. The great loss of sodium which follows adrenalectomy takes place through the kidneys.

serum potassium. They also showed that the injection of sodium chloride prolonged life more than did salts of other cations or solutions of glucose. In 1932, we found at the Presbyterian Hospital<sup>3-5</sup> in patients with decompensated adrenal insufficiency (adrenal crises) that the state of dehydration in these individuals was associated with a constant decrease in the concentration of sodium in the blood and a less constant increase in potassium. The concentration of sodium may fall from a normal value of about 140 m. eq per l. to a level of about 100 m. eq per l. and potassium may rise to about 10 m. eq per l., a little more than double the normal concentration. The decrease in serum sodium is accompanied by a corresponding drop in chloride, bicarbonate, or both. We also pointed out the importance of the use of sodium salts and water in correction of these disorders and showed that an adrenal crisis might be induced by the simple process of the withdrawal of the sodium ion from the diet. The changes observed in the first patient of this study are shown in Table 1. Finally, we were able to demonstrate that the

TABLE I

## CORRELATION OF BLOOD CHANGES WITH SALT FEEDING AND SALT WITHDRAWAL IN A PATIENT WITH ADDISON'S DISEASE

Date	Na m eq per l	K m eq per l	Cl m eq per l	HCO <sub>3</sub> m eq per l	$\frac{\text{Non}}{\text{Protein}} \text{ Nitrogen}$ mg per 100 cc	Blood Pressure	Remarks
July 19 1932	123.5	5.3	88.6	21.8	39.0	85/55	Blood taken shortly after admission Profound weakness and vomiting
July 26	107.8	7.1	72.7	21.5	45.0	65/48	Critically ill Almost in extremis No therapy up to this time
Aug. 2	133.0	5.1	93.8	27.5	20.6	84/60	Treated with a single dose of Eschatin and then NaCl daily No more vomiting, sitting up
Nov. 14	139.9	4.6	107.3	24.3	20.0	112/71	Up and about at home, doing part of housework Eats 7 guns of NaCl daily plus diet Slight puffiness of eyelids
Jan. 24 1933	126.8	5.7	92.3	21.2	35.0	86/60	After 7 days salt-poor diet, weak and vomiting frequently Confined to bed
Jan. 30	138.0	5.0	103.5	25.9	25.0	122/80	After no further treatment except NaCl added to diet and given by rectum No vomiting Much stronger

decrease in sodium concentration in the blood serum was associated with an increase in the excretion of this base and water by the kidneys, perhaps as a result of a decrease in their reabsorption by the renal tubules. The order of magnitude of the sodium excretion suggested that it was lost from the interstitial fluid of the tissues as well as from the blood. Harrop<sup>6,7</sup> confirmed these observations and, simultaneously with Allers and Crandall,<sup>8</sup> showed that completely adrenalectomized dogs could be maintained in good health for many months without the use of cortical extract if given large amounts of sodium chloride to which was added sodium bicarbonate or citrate. *Thus, the presence of a defect in sodium metabolism in adrenal insufficiency in man and animals has been clearly established and it has been shown that the administration of sodium salts and water may re-establish adrenal compensation.*

A reduction in the sodium concentration in the body alone without a concomitant decrease in blood volume and interstitial fluid does not, however, give rise to the picture of adrenal insufficiency. For example, in a patient with mild adrenal insufficiency who was maintained in moderately good health by the oral administration of salt and water by Willson and Sunderman,<sup>9</sup> the restriction of water ingestion resulted in the precipitation of a crisis accompanied by a sharp decrease in blood plasma volume. It is noteworthy that the serum sodium level, which was abnormally low before water restriction, rose to normal with the onset of the crisis as a result of a decrease in the water content of the plasma. This finding aids in the explanation of the observation of Winter et al.,<sup>10</sup> who induced rapidly fatal adrenal insufficiency in cats by interrupting the supraopticohypophyseal tract and subsequently removing the adrenal glands. In these animals with diabetes insipidus, adrenal insufficiency developed despite the fact that the sodium content of the blood remained normal and while the potassium content increased. It is probable that in these cats death resulted from shock associated with a decrease in plasma volume.

### POTASSIUM METABOLISM

Accompanying the decrease in serum sodium concentration and the loss of water with the development of adrenal insufficiency there is usually, as has been stated, *an increase in the concentration of potassium*. The importance of the abnormality of potassium metabolism in adrenal insufficiency is becoming more and more impressive. Kendall and Allers,<sup>11</sup> as well as Zwemer,<sup>12</sup> have demonstrated the abnormal susceptibility of adrenalectomized animals to the ingestion or injection of small amounts of potassium salts, and Wilder, Snell and their collaborators<sup>13</sup> have indicated the danger attendant upon the ingestion of large amounts of potassium salts by patients with Addison's disease. The latter investigators have shown that one deleterious effect of potassium salts results from the fact that they tend to augment the excretion of the sodium ion. Another reason for the toxic effects resulting from the ingestion of liberal amounts of potassium salts is the retention of potassium in the blood serum above the normal level of 4 to 5 m. eq. per l. This develops, apparently, because of failure to excrete potassium as rapidly as normal.

It has been maintained by some that the increase in potassium in the blood is responsible for the adrenal crisis. This concept appears to be

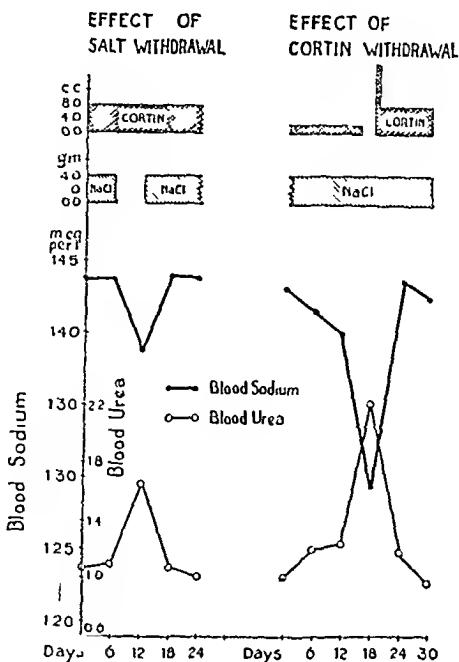


Fig. 5.—Qualitative similarity of the effect of the withdrawal of salt and cortin in the adrenalectomized dog. The behavior of potassium parallels that of blood urea.

untenable because, as has been stated, there is often no increase in serum potassium in patients with Addison's disease whereas in other disease states, in which potassium is often retained, e.g., renal insufficiency, the clinical picture of adrenal insufficiency is not present.

### RENAL FUNCTION

In 1916 Marshall and Davis<sup>14</sup> noted an increase in non-protein nitrogen in the blood of adrenalectomized animals and were the first to suggest that the adrenal glands exert an influence on renal function. In patients suffering from Addisonian crises there is often some retention of non-protein nitrogen, the highest value observed by us being 102 mg per 100 cc. This disturbance can be corrected by the administration of salt and water, but even when the sodium concentration reaches a normal level a decrease in the urea clearance may persist. Recent work of Margitay-Becht and Gomori<sup>15</sup> indicates that this disturbance in renal function results at least in part from a decrease in renal blood flow and in glomerular filtration as measured by creatinine clearance tests.

Studies of Stahl, Kuhlmann and Urban<sup>31</sup> suggest a similar conclusion. In severe adrenal insufficiency, there may also be retention of phosphate and sulphate and a decrease in the formation of urinary ammonia. Whether a decrease in renal blood flow alone accounts for the decrease in ammonia formation or whether a specific disturbance in nitrogen metabolism is responsible for it is not known. It seems certain that the disturbances in sodium and water metabolism are, at least in part, dependent on faulty renal mechanism which results from a lack of cortical hormone. Furthermore, Harrison and Darrow<sup>16</sup> believe that they have demonstrated in adrenal insufficiency a specific disturbance in renal function insofar as the normal regulation of potassium excretion is concerned.

#### CARBOHYDRATE METABOLISM

Since Porges<sup>17</sup> in 1909 first demonstrated the presence of hypoglycemia in patients with Addison's disease as well as in adrenalectomized animals, it has been recognized that a *disturbance in carbohydrate metabolism* exists in adrenal insufficiency. A decrease in glycogen storage has been emphasized repeatedly by Britton and Silvette<sup>18</sup> and the sensitivity of the Addisonian patient to the injection of small doses of insulin is well established. The studies of Britton and those of Long and his associates<sup>19</sup> have demonstrated that glycogen storage in the liver of adrenalectomized and also normal animals is increased by the injection of potent cortical extract or of certain crystalline steroids isolated from the adrenal glands, notably corticosterone in contrast to desoxycorticosterone.

In most patients with Addison's disease there is mild hypoglycemia. Thus, among a group of twenty-three of our patients the fasting blood sugar level at some time was found to be below 80 mg per cent in sixteen, in nine it was below 70 mg, and in five there were classical severe hypoglycemic episodes associated with blood sugar levels below 50 mg per cent. This hypoglycemia cannot be correlated with the concentration of sodium or potassium in the blood. On the other hand, Long<sup>19</sup> has recently presented convincing evidence indicating that, in the rat, at least, certain crystalline substances, obtained from the adrenal cortex, which are active in correcting the salt and water disturbances are also active in their action on carbohydrate metabolism. Kendall<sup>20</sup> has recently presented evidence suggesting that an antagonistic action exists between

insulin and adrenal cortical hormone and that, in the absence of the latter, there is a flow of potassium and glucose to tissue cells similar to that following insulin administration On the other hand, in the diabetic rat, Kendall reports that the administration of cortical extract increases the urinary excretion of potassium in addition to augmenting glucose elimination as earlier demonstrated by Long<sup>19</sup> It is Long's<sup>21</sup> contention that the increase in potassium excretion results from the increase in protein breakdown and gluconeogenesis stimulated by certain steroids of the adrenal cortex

#### MISCELLANEOUS DISTURBANCES

Certain other physiological disturbances, secondary to the abnormalities of electrolyte and water metabolism, are present in the adrenal crisis and contribute to the picture of dehydration and shock These include a decrease in plasma volume, a fall in blood pressure to levels of shock, a decrease in blood flow, acrocyanosis and hemoconcentration Occasionally fatal adrenal insufficiency develops with evidence of hemoconcentration, peripheral vascular collapse and fever but without demonstrable abnormalities of the electrolytes and glucose of the blood The underlying explanation in these instances remains obscure but dehydration with relative retention of sodium, as in the patient of Willson and Sunderman, may constitute the mechanism involved

Whereas the decreases in plasma volume and peripheral blood flow as well as disturbances in carbohydrate metabolism constitute factors contributing to the asthenia of the Addisonian patient, it seems likely that certain unknown mechanisms are also involved This idea is supported by the important observations of Ingle<sup>22</sup> which show that despite the simultaneous treatment of adrenalectomized rats with salt, corticosterone and desoxycorticosterone, the capacity of these animals for muscular work continues at a level strikingly lower than that of sham-operated animals

A number of neurological disturbances, both focal and diffuse, may occur in the course of adrenal insufficiency In certain instances these may result from hypoglycemia, in others hypotension and a decrease in cerebral blood flow may play a part Whether or not other factors may be present is not known

Hypercalcemia is at times present in adrenal insufficiency and cannot be ascribed to hemoconcentration alone Bilirubinemia, elevation of

serum phosphatase and retention of bromsulphalein have also been encountered. The reason for these disorders and the mechanism underlying the disturbances of pigmentation in Addison's disease are not understood.

Verzár<sup>23</sup> has recently ascribed the basis for physiological disturbances in adrenal insufficiency to a failure of the important function of phosphorylation. This function among other activities is responsible for the formation of respiratory ferment from its precursor riboflavin, i.e., vitamin B<sub>2</sub> and for the specific absorption of glucose, levulose and fat from the bowel. However, the validity of this attractive hypothesis seems extremely doubtful in the light of recent studies, particularly those of Ferrebee<sup>24</sup> who has shown that the ability to phosphorylate vitamin B<sub>1</sub> is retained in completely adrenalectomized rats.

#### TREATMENT

I should like now to consider the problem of the treatment of Addison's disease. The treatment of Addison's disease, like that of diabetes mellitus, should be directed primarily toward (1) the specific replacement of the hormone or hormones lacking, (2) the correction of the physiological disturbances which ensue as a consequence of this endocrine deficiency, and (3) the avoidance of factors known to intensify manifestations of the disease. The nature of the therapy and the vigor with which it must be applied vary tremendously with the phase of the disease present. In the patient whose disease is well compensated, a few general measures such as the avoidance of physical and mental fatigue, the immediate care of even mild acute infections, and the ingestion of a liberal amount of sodium chloride will suffice to maintain moderately good health for periods of months or even years. On the other hand, with the appearance of a crisis, whether it appears in the natural progression of the disease or whether it results from known causes, a number of active therapeutic measures must be applied promptly and intensively in order to combat successfully the grave and often fatal loss of inorganic base with its attendant dehydration and peripheral circulatory collapse. Procrastination or inadequate treatment of the crisis sacrifices patients who might otherwise be restored to a useful existence.

Before proceeding with the discussion of therapy, I should like to digress for a moment to make a plea that the treatment of adrenal insufficiency in man be limited to patients who can be shown to be suffering from that condition. This is meant to be neither trite nor flippant, but

we continue to see a large number of patients, mostly asthenic, tired women, who have received injections of 2 to 3 cc of certain commercial extracts daily or perhaps once a week. It is unlikely that this treatment does harm but it is certain that it is costly and totally ineffective beyond its action as a placebo. The treatment of cortical adrenal insufficiency is directed primarily at disturbances of water and electrolyte metabolism. If these are not obviously present or if they cannot be made manifest by placing the suspected patient upon a salt-poor regime, under close observation for 1 to 7 days, there can be little or no reason for instituting the treatment of Addison's disease.

With the recognition of the disturbances in electrolyte and water metabolism present in adrenal insufficiency and as a result of the introduction of salt treatment,<sup>4</sup> the unhappy plight of the Addisonian patient was to a certain extent bettered. The introduction of the low potassium diet by Wilder and his colleagues<sup>13</sup> constituted a further theoretical improvement. The preparation of extracts of the adrenal cortex for use in patients gave much promise and in large amounts they have been demonstrated by Thorn and others<sup>25</sup> to have undeniable physiological activity. Nevertheless, I think we will all agree that in doses which patients can afford or tolerate, the results of treatment have by and large been disappointing.

In the past year, the synthesis of desoxycorticosterone by Steiger and Reichstein<sup>26</sup> in Zurich has made available for use in patients a natural steroid of the adrenal cortex which has easily demonstrable physiological activity. While this chemical entity is, as already mentioned, only one of a series of known active steroids in the cortex and while there are other substances of far higher potency not yet identified chemically, this steroid has shown itself to be of extraordinary importance in the treatment of adrenal insufficiency. In addition to this advance of significant practical value we have learned much concerning the nature of the physiological disturbances resulting from adrenal cortical insufficiency by observing the changes brought about by the administration of a single chemical substance, i.e., one of the esters of desoxycorticosterone.

In this country, Thorn<sup>25,27</sup> was the first to use desoxycorticosterone and he has contributed greatly to the practical aspects of the treatment of Addison's disease with the implantation of pellets. His studies have also added to our knowledge of the action of desoxycorticosterone. Our own results are in general agreement with those obtained by him as well

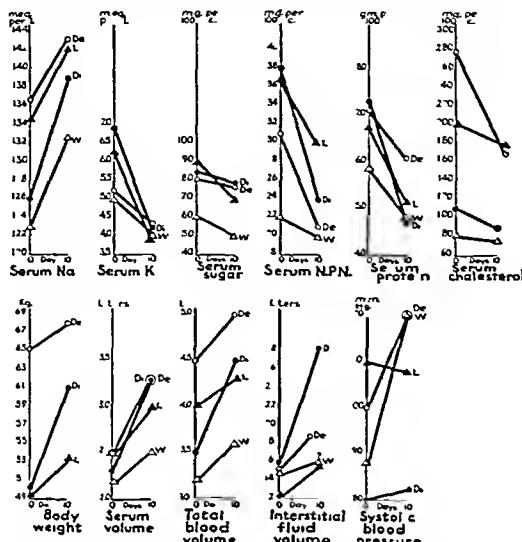
EFFECT OF TEN DAYS TREATMENT WITH  
DESOXYCORTICOSTERONE PROPIONATE

Fig 6.—Effects produced in Addisonian patients in 10 days by a desoxycorticosterone derivative. These patients received large doses, i.e., about 190 mg., during initial 10 days of treatment.

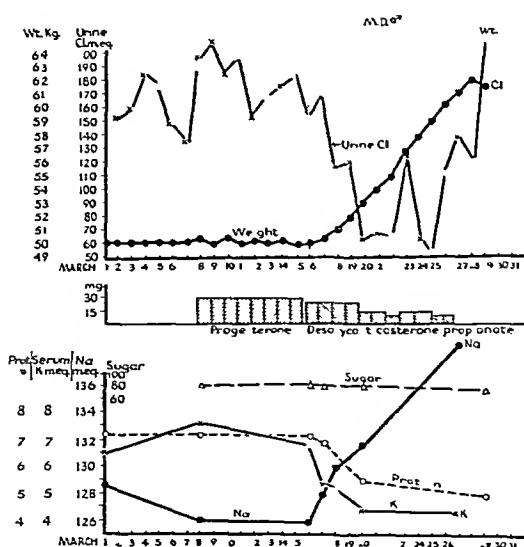


Fig 7.—A comparison of the effects of progesterone and desoxycorticosterone in a patient with Addison's disease.

as those reported by Cleghorn and his associates<sup>28</sup> and amplify those of Levy Simpson<sup>29</sup> in England

At the Presbyterian Hospital, Drs Ferrebee, Ragan, Atchley and I<sup>30</sup> have in the past 10 months had eighteen patients with Addison's disease under treatment with esters of desoxycorticosterone furnished by the Roche-Organon laboratories. In our studies we have employed both the acetate and propionate of desoxycorticosterone which have been administered subcutaneously or intramuscularly in peanut oil. Results of the administration of desoxycorticosterone may be summarized as follows

#### SALT AND WATER METABOLISM

Desoxycorticosterone esters cause a striking retention of salt and water. The rate of retention of the sodium ion usually exceeds that of water so that as a rule the serum sodium concentration rises to normal and is maintained at normal level as fluid retention continues. In a few instances, water is retained more rapidly than sodium so that the sodium concentration of the blood may actually fall for a few days. In one of our patients with extensive tuberculosis, it was never possible to raise the sodium concentration above 132 m eq per l although the retention of water was sufficient to be associated with pulmonary congestion, hydrothorax, generalized edema and temporary elevation of venous pressure.

The amount of salt and water retained varies greatly in different patients and cannot be correlated with the initial sodium or serum protein concentration or with the initial plasma volume. One of our patients gained 11 kilos in 10 days during which time he received 190 mg of hormone. In contrast, another patient gained but 2 kilos in 30 days during which time he received 725 mg of hormone. Both patients received the same amounts of sodium and potassium salts in their diets.

Coincident with the retention of salt and water and with the gain in weight there appears a considerable decrease in the urinary excretion of sodium, chloride and water. For example, in one of our patients the urine output fell from an average of 1500 cc daily to as little as 410 cc during the period of administration of 15 mg of hormone each day. The sodium excretion fell from a level of about 160 m eq to 28 m eq in 24 hours and the chloride excretion underwent a commensurate change.

As a result of these changes, there is marked increase in extracellular fluid volume as measured by the thiocyanate method. The blood plasma

volume in those patients in whom it was measured increased between 300 and 1200 cc during the first ten days of treatment with hormone. These changes were in close agreement with decreases in hematocrit and serum protein concentration. In two patients, the serum protein concentration fell from 7.3 to 4.7 and from 5.9 to 4.8 per cent respectively. There were no consistent changes in albumin/globulin ratio associated with this dilution of the blood.

### POTASSIUM EXCRETION

Synthetic desoxycorticosterone esters cause a striking decrease in the concentration of the potassium in the serum and frequently reduce it to abnormally low levels. Thus, in nine out of a group of ten patients, the potassium concentration after treatment was below 4 m eq per l, the lower limit of our normal values. In two patients, potassium has reached a level of 2.9 and 2.4 m eq per l respectively.

The urinary excretion of potassium increases regularly on the first day of hormone injection and thereafter it becomes variable. The potassium excretions cannot be satisfactorily correlated with changes in nitrogen excretion as might be expected if the increase were due solely to the destruction of body protein for gluconeogenesis.

### NITROGEN EXCRETION

The non-protein nitrogen level of the serum decreases even when it is within normal limits at the beginning of treatment.

Total nitrogen excretion may not be affected but as a rule there is a slight increase not exceeding 2 grams in the first 2 or 3 days of therapy. Ammonia excretion appeared to increase within 24 hours after administering desoxycorticosterone in the two patients in whom determinations were made before and after treatment.

### BLOOD CALCIUM AND CHOLESTEROL

The serum calcium concentration decreases following the administration of synthetic hormone. This was observed to be true in each of six patients in whom determinations were made before and after 10 days of therapy. This change may be attributed to hemodilution with its attendant decrease in serum albumin concentration.

The cholesterol content of the blood also decreases, at least in part as a result of hemodilution.

## CARBOHYDRATE METABOLISM

No evidence has been found in our studies to suggest that desoxycorticosterone esters have any effect on carbohydrate metabolism in our patients with Addison's disease. After 10 to 40 days of treatment the fasting blood sugar level is often as low as or even lower than before. In one patient who received the enormous dose of 25 mg of hormone daily for 30 days the fasting blood sugar level was 74 mg and 4 hours after the ingestion of 100 grams of glucose it fell to 46 mg per cent. The respiratory quotients, measured on 2 days before and again on 2 days after 2 weeks of hormone treatment in this patient, were 0.85 and 0.78 respectively, indicating a change of questionable significance. In another patient receiving 10 mg of hormone daily, severe hypoglycemia with blood sugar levels of 40 and 38 mg per cent were observed on successive days after 2 weeks of treatment. The dose of hormone in this patient was insufficient to raise the blood sodium to normal though it was adequate to cause excessive fluid retention.

## BLOOD PRESSURE

The effect of desoxycorticosterone esters on arterial pressure is dramatic even though it does not appear as promptly as do the effects on salt and water metabolism. The blood pressure has reached normal in all of our patients in the course of 2 to 4 weeks and has risen gradually to 175/110, 160/92, 160/110 and 146/108 in four patients. In only one of these patients was there, on the basis of history, evidence of hypertensive vascular disease antedating the onset of Addison's disease.

## PIGMENTATION

No definite effect on pigmentation has been noted in any of our patients beyond that which may be attributed to rehydration.

## COMPLICATIONS

In view of the high degree of physiological activity of desoxycorticosterone esters, it could be anticipated that overdosage might result in the appearance of disturbing complications. Indeed, fifteen of eighteen patients developed edema varying from mild and transient puffiness of the face and ankles to massive anasarca. In five patients there developed varying degrees of respiratory distress, a sense of tightness in the chest



Fig 8—X-ray of heart of an Addisonian patient before treatment

associated with x-ray evidence of dilatation of the heart predominantly on the right side. In four of these five patients, there was an elevation of venous pressure which reached levels from 110 mm to 250 mm. In three in whom determinations were made there was a striking decrease in vital capacity associated with definite evidence of pulmonary congestion on x-ray examination. In four of the five patients developing cardiac dilatation and congestive failure, prompt relief resulted from the limitation of sodium chloride intake to that present in the diet and in certain instances with reduction in the dose of desoxycorticosterone. One patient who had been taking 15 mg of hormone every other day and had added

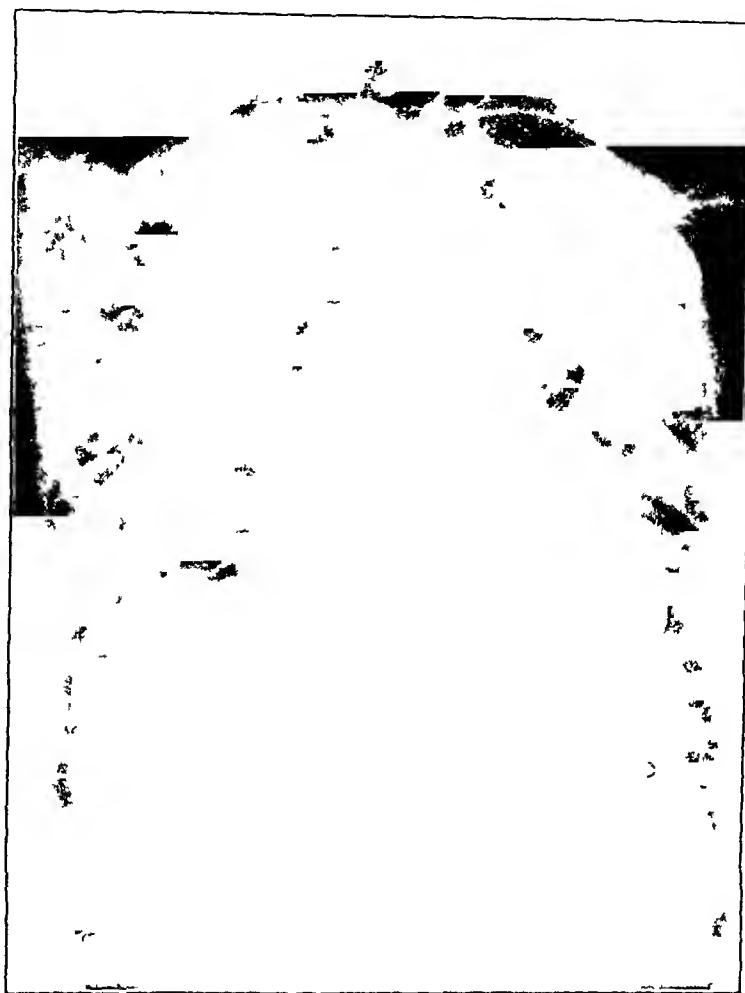


Fig. 9—X-ray of heart of the same patient as in Fig. 8 after excessive treatment with desoxycorticosterone acetate and salt

2 to 3 teaspoons of salt to his diet received some relief from limitation of salt and water and a phlebotomy but succumbed with terminal bronchopneumonia. Autopsy revealed dilation of the heart with mild hypertrophy and a curious swelling of the muscle cells and their nuclei in the right ventricle.

The mechanism for the development of cardiac insufficiency in these patients is not clear. It is certain that it does not result from an increase in arterial pressure alone because in three of our patients congestive failure appeared when the blood pressure was below 110 mm. Hg. A rapid

and extensive increase in circulating blood volume is a possible factor, although in one patient the increased blood volume caused by the hormone was only 300 cc at the time when the venous pressure was elevated and the symptoms were most marked. The possible relation of the decrease in potassium concentration is inescapable but its significance is not known. There is no evidence of vitamin B<sub>1</sub> deficiency as an etiological factor with the exception of relatively low excretion of thiamin in the urine of some of these patients.

The complications which have been discussed serve to indicate the dangers attendant upon the use of desoxycorticosterone esters and I think that they are of sufficient gravity to justify a warning concerning their indiscriminate or uncontrolled use.

#### RESULTS OF TREATMENT

It is beyond the scope of this paper to discuss the details of treatment. I might, however, say a few words concerning our experiences. Four out of eighteen patients who have been under treatment with synthetic hormone in the past 10 months have died. One of these succumbed secondary to cardiac insufficiency, as has been stated. Another died with advanced tuberculosis. Two died suddenly at home and information obtained has not been sufficient to interpret the cause of death. One other patient died unexpectedly while under observation in the hospital. She had had mild cardiac insufficiency of the type already described and her blood electrolyte pattern except for slight depression of the potassium level was essentially normal 3 days before death. The night before her death she had a rise in temperature to 103° associated with vomiting and slight sore throat but the next morning, except for mild symptomless hypoglycemia (her blood sugar was 62 mg per cent), she appeared well. On rounds, she gagged mildly while having her throat examined and fell back on her pillow dead. Autopsy afforded no explanation for her sudden demise. The remaining patients have made extraordinary gains as far as their sense of well-being, their strength, their appetite, their weight, and their outlook on life are concerned. Some are at work and others are, from the point of view of strength, capable of undertaking their normal activities. It must be remembered, however, that the majority of patients with Addison's disease are suffering not only from adrenal insufficiency but also from tuberculosis which offers a therapeutic problem in itself.

The individual hormone requirements of patients with adrenal insufficiency vary widely and our patients appear to need as a maintenance dose between 1 and 10 mg daily administered in peanut oil under the skin. It seems to us that the dangers of cardiac insufficiency may be greatly diminished if the dose of hormone is sufficiently great so that the patient will not require a salt intake in excess of the normal diet. The treatment of the acute crises requires the parenteral administration of glucose in normal salt solution and the administration probably in most instances of about 25 mg of hormone daily for a period of 3 or 4 days. The blood sodium level, the arterial pressure, the venous pressure and the patient's general condition must serve as the guides to dosage.

In conclusion it may be reiterated that in recent years a great deal has been learned concerning the nature of the disturbances present in adrenal insufficiency. While many of these appear to be related directly or indirectly to disturbances in electrolyte and water metabolism or to abnormalities in carbohydrate metabolism, there remain innumerable problems which have not been solved.

With the synthesis of desoxycorticosterone there has been made available a valuable therapeutic agent for the correction of disturbances in electrolyte and water metabolism in adrenal insufficiency. This synthetic hormone offers considerable hope for the future of those individuals suffering from Addison's disease, but it seems likely that other substances will become available which will find wider application in the correction of the multiple disorders present.

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## THE CUSHING SYNDROME, NEOPLASMS OF THE ADRENAL GLAND \*

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WE OWE a great debt to Dr Harvey Cushing<sup>1</sup> for his careful delineation in 1932 of the clinical syndrome which now bears his name. Such a striking picture could not escape notice and there are earlier references to some of its features. Hippocrates<sup>2</sup> said of Phoetas, wife of Pythias, that she lost her periods, became masculinized and developed a beard. The first definite case is the often misquoted one of William Cooke,<sup>3</sup> who reported, in 1811 under the title "A Case of Internal Hydrocephalus," the findings in a child who presented plethoric obesity, hirsuties and an enlarged clitoris. At postmortem examination there was found a tumor in the region of the right adrenal gland. Although Thornton<sup>4</sup> in 1890 had removed an adrenal tumor from a woman and had seen hirsuties disappear, it was not until 1904 that Bulloch and Sequeira<sup>5</sup> clearly outlined the relation of the adrenal gland to virilism. Apert,<sup>6</sup> in 1910, collected a considerable series of cases and confirmed the view that the obesity, amenorrhea and hirsutism were of adrenal origin. In 1921 Achard and Thiers<sup>7</sup> described their cases of "diabète des femmes à barbe" in which the association of diabetes, amenorrhea and hirsutism was noted. This then, in brief, was the state of our knowledge in 1932 when Cushing published his excellent report. He sharply outlined a clinical picture consisting of a rapid, plethoric, painful obesity affecting primarily the face, neck and abdomen, but usually sparing the limbs, thus giving rise to an obesity of the buffalo type. The facial changes made the eyes appear small and slit-like, the so-called "pig eyes." There was acrocyanosis of the extremities with purplish lineae atrophicae on the thighs and the lower part of the protuberant abdomen. Hirsuties was marked and necessitated shaving by the women affected. There was a tendency toward polycythemia and hypertension, and glycosuria was a frequent finding, as was hypercholesterolemia. There was mus-

cular weakness and osteoporosis which led to a cervicodorsal kyphosis with shortened stature. Occasionally, the osseous changes led to pathological fractures. Amenorrhea was present in the females and impotence in the males. In addition there was a marked susceptibility to infectious processes, particularly of the skin. Mental changes seemed to be an integral part of the syndrome, and fully developed psychoses were seen. Renal damage, including malignant nephrosclerosis, has been noted.<sup>8</sup>

Cushing attributed this clinical picture to the presence of a functioning basophilic adenoma of the anterior lobe of the pituitary gland and he reported clinical regression after  $\gamma$ -ray treatment to the hypophysis.

In 1935 Oppenheimer and I<sup>9</sup> reported a patient we had observed in 1932 who presented all the features described by Cushing. At postmortem examination, the pituitary gland revealed no tumor even on serial section. There was, however, a large carcinoma of the adrenal cortex. At that time and again in 1937<sup>10</sup> we reviewed the literature and concluded that there were no clinical features by which we could differentiate cases of Cushing's syndrome due to an adrenal tumor from those due to a basophilic adenoma of the pituitary.

Our clinical material consists of seven patients who all presented typical clinical features of Cushing's syndrome. These features need not be detailed again, but all of the patients were undoubtedly cases of the disease as you can see in the photographs (Figs. 1 to 6).

Of these seven patients, four were operated upon and the following were the operative findings:

One case of carcinoma of the adrenal cortex

Two cases of adenoma of the adrenal cortex

One case of normal adrenal glands (the only male case)

Two patients died on the medical wards and at postmortem examination there was found in one, a carcinoma of the adrenal cortex, in the other, simple hyperplasia of the adrenal glands, combined weight 244 grams. We were unable to complete our studies of the seventh case. An eighth case due to an adrenal carcinoma has been seen since this report was prepared. Of the four patients operated upon, all died. We were unable to secure permission to examine the pituitary gland in the three patients who had adrenal new growths. The pituitary gland revealed no tumor on serial section in the fourth case, that is, the male with normal adrenal glands at operation and postmortem. One of the patients operated upon, the patient with an adrenal carcinoma, survived the operation.



Fig 1



Fig 2



Fig 3



Fig 4



Fig 5



Fig 6

Fig 1 Author's case, Cushing's Syndrome, due to adrenal cortical carcinoma

Fig 2 Author's case, Cushing's Syndrome, due to adrenal cortical adenoma

Fig 3 Cushing's case, Cushing's Syndrome, due to bisophilic adenoma of the pituitary

Fig 4 Turnbull's case, Cushing's Syndrome, due to thymic carcinoma with adrenal cortical hyperplasia

Fig 5 Wieth-Pedersen's case, Cushing's Syndrome, due to sarcoma (?) of the pituitary, adrenal cortical hyperplasia

Fig 6 Author's case, Cushing's Syndrome, no anatomic lesion in any of the endocrine glands

for two months. In this period a remarkable improvement took place. The plethoric obesity of her face disappeared, the blood pressure returned to normal levels, the menses returned and the glucose tolerance improved. The restoration toward normal was striking, and there was no doubt that it was the result of the removal of the adrenal tumor.

Of the seven patients studied by us, four had tumors of the adrenal glands, two had no tumors either of the adrenal or pituitary glands, and the seventh could not be followed. No one of our three patients whose pituitary glands we could examine showed a basophilic adenoma.

#### HIRSUTISM AND THE DIFFERENTIATION OF THE VARIOUS TYPES

The most striking single clinical feature in the symptom complex under discussion is the presence of hirsuties. This is particularly marked in the females who constitute a great majority of the cases so far reported.

From a pathologic-anatomic viewpoint there are five groups of lesions associated with hirsuties, namely:

- 1) Pineal tumors, usually teratomas
- 2) Ovarian tumors (arrhenoblastomas of Robert Meyer)
- 3) Thymic tumors
- 4) Adrenal cortical tumors
- 5) Basophilic tumors of the pituitary (Cushing)

There is an additional group of cases in which hirsuties is a prominent feature and at autopsy no anatomic evidence can be found in any of the endocrine glands to explain its presence. This "idiopathic group" has been known for a long time and in its minor forms may be seen daily in any obesity or endocrine clinic. These patients are characterized by their general well-being, the failure of their symptoms to progress, and the absence of any physical or laboratory findings to explain their complaints. When they present only hirsuties and obesity they are merely cosmetic problems and are left alone, but when they show progressive deterioration, loss of sexual power, hypertension, osteoporosis and other features of well-developed basophilism, they are very difficult problems in diagnosis and therapy. That even complete, typical cases of Cushing's syndrome may present no tumor formation in any of the endocrine glands is proved by two of the patients in our series and other cases in the literature.

The hirsutism of pineal lesions usually presents no diagnostic diffi-

culties with regard to pituitary basophilism. The cases are almost all examples of pubertas praecox in young boys. The typical obesity with striae is absent, hypertension is uncommon, and the signs of an intracranial lesion usually make the diagnosis fairly obvious.

The arrhenoblastomas of Robert Meyer present hirsuties as a leading symptom, but obesity and hypertension are not usually associated. These patients, as a rule, should present no problem, but if either obesity or hypertension, or both, should be associated with the hirsutism due to the ovarian growth, the differential diagnosis from pituitary basophilism might not be easy. This is especially true when it is recalled that the ovarian tumor may escape detection by physical examination.

The patients with thymic tumors who present hypertrichosis are particularly interesting. The three recorded examples presented practically all the features outlined by Cushing as occurring in pituitary basophilism. In fact, in one case the findings were so suggestive as to lead Cushing himself to predict that a basophilic adenoma would be found as the anatomic lesion. Serial sections of the pituitary revealed no tumor or basophile preponderance, but marked adrenal cortical hyperplasia was found in all three of these cases of thymic tumor. It is probable that the clinical features were a manifestation of the adrenal hyperplasia. The literature contains many examples, including our own, of patients who presented all the features of Cushing's syndrome clinically. At postmortem these showed normal pituitary glands so far as tumor formation is concerned but marked changes in the adrenal cortex consisting of cortical adenoma, cortical carcinoma or simple cortical hyperplasia.

To complete the pathological variations, typical cases of Cushing's syndrome have been reported where the only lesion found was the one predicted by Cushing, namely, a basophilic adenoma of the pituitary. This lesion has been present alone in several of Cushing's cases and in others reported in the literature. Pardee,<sup>11</sup> in a relatively recent review, is of the opinion that the basophilic adenoma is the basis for the syndrome. We cannot, however, agree that osteoporosis is of any value in the exclusion of cases of adrenal origin. We have seen marked generalized decalcification of bone with pathological fractures in cases due to proved adrenal tumors.

At this point I should like to show you photographs of seven patients who presented typical examples of Cushing's syndrome clinically. I



Fig 7.—Perirenal insufflation of air showing tumor of adrenal gland

think you will agree that the patients present a remarkable similarity, yet each one had an entirely different lesion pathologically. There can be no doubt, that we are dealing with a clinical syndrome, not a pathological entity and yet there must be some underlying common denominator in all these varied lesions to result in such clinical similarity. We believe that denominator to be altered adrenal function (Figs 1 to 6).

There have been several clinical and laboratory aids that seem to be of some use in studying these cases. First, Cahill and later, Mencher have been very successful in delineating the size of the adrenal glands and the presence or absence of an adrenal tumor by  $\alpha$ -ray examination after the injection of air into the perirenal tissues. Figure 7 is the roentgenogram of one of our cases in which the tumor was demonstrated and later removed surgically (Fig. 7).

In 1934 Robert T. Frank<sup>12</sup> demonstrated the presence of greatly increased estrogenic activity of the urine in cases of Cushing's syndrome due to an adrenal cortical carcinoma. This finding has been confirmed for the group here reported. Interestingly enough, it was not present in the two cases of benign cortical adenoma studied.

In 1933 Broster and Vines<sup>13</sup> reported a specific staining reaction for the cells of the adrenal cortex in cases of virilism. They stated that the cortical cells stained a deep red when treated with the Ponceau-fuchsin stain, the so-called "fuchsinophilic reaction." Later studies have failed to substantiate the specificity of this reaction.

In 1935 Crooke<sup>14</sup> reported that the only constant pathological feature in all the cases of Cushing's syndrome that he could study was a peculiar hyalinization and vacuolization of the cytoplasm of the basophile cells of the pituitary gland with the disappearance of the normal granular structure of the cytoplasm. He found this change in Cushing's original cases, in the cases due to thymic tumors and in some cases due to adrenal tumor or hyperplasia. The change was present in the cells of the anterior lobe, and not in the cells of the basophile tumor itself in those cases in which a basophile adenoma was present. Crooke found this change in every case of basophilism which he could study and states that it is the anatomic basis for the syndrome. This hyalinization of the basophile cells was present in all three of our own cases which were studied. Gellerstedt<sup>15</sup> confirmed this finding and added that in his opinion "the basophile adenoma has no significance as an etiological factor in Cushing's syndrome." More recently Ecker<sup>16</sup> studied 721 pituitary glands from normal subjects and found the change described by Crooke in only 11 per cent. He also found the same alteration in 55 per cent of seventy-two basophilic adenomas from patients who did *not* present Cushing's syndrome. Ecker concludes "It appears, therefore, unwarranted to consider hyalinization as invariably associated with the state designated as pituitary basophilism." Nevertheless one is struck by the low incidence of the changes noted by Crooke in this large control series and the high incidence in basophilism. It seems to me that the changes described by Crooke are significant.

In 1939 Crooke and Callow<sup>17</sup> reported the excretion of large amounts of androgenic substances and the presence of trans-dehydro-androsterone in the urine of patients suffering from Cushing's syndrome due to malignant adrenal tumors. These androgens were not present in excess in similar clinical cases due to other lesions. They suggest that excessive androgen excretion, which can be approximated by a simple colorimetric test, indicates an adrenal tumor in cases of Cushing's syndrome. They were unable to confirm Frank's finding of increased estrogenic substances in their two cases.

*Prognosis and Treatment* The condition is a serious one. Most of the patients survive only several months to several years, although Cushing himself described a patient alive after 22 years, and Rolleston quotes a patient of Maranon's alive after 17 years. Obviously, the prognosis varies with the pathologic basis of the syndrome and not too much can be expected in patients suffering from malignant disease of the adrenal, thymus or pituitary.

Cushing recommended radiotherapy to the pituitary gland and reported very striking results. Other observers have confirmed his observations, but this therapy frequently is unavailing. Because the pituitary tumors are usually very small, surgical approach is rarely indicated, although it has been attempted and radium has also been implanted directly into the hypophysis after surgical exposure.

It is in those cases of Cushing's syndrome due to an adrenal lesion that it is particularly important to make an early diagnosis, because it is in this group that brilliant surgical results have been achieved with complete restoration to normal. It is obvious that early recognition is particularly vital in malignant diseases if we are to expect favorable results. We are fortunate in possessing several direct leads enabling us to detect the adrenal cases and we wish to enumerate them now for emphasis.

- 1) Perirenal and periadrenal insufflation of air with x-ray photographs, pyelographic studies are an additional aid
- 2) Biologic assay of urine for estrogens
- 3) Biologic and chemical assay of urine for androgens

In addition, this group is rare in men, occurs in women and is most frequent in female children.

All who have had surgical experience with these patients are aware of the very high operative mortality. We have attempted to reduce this by active treatment to combat surgical shock and adrenal failure, and have used large doses of adrenal cortical hormone postoperatively.

In closing this part of the discussion greatest credit should be given the contributions of Harvey Cushing to this subject. Even if "basophilism" in a strict sense is not the entire answer to the problem, we are all indebted to Cushing for his clear clinical delineation of the syndrome and for our renewed interest in it.

In the preceding discussion I have considered some tumors of the adrenal cortex which present endocrine disturbances as clinical features. Professor Young will present some other clinical features of hyper-

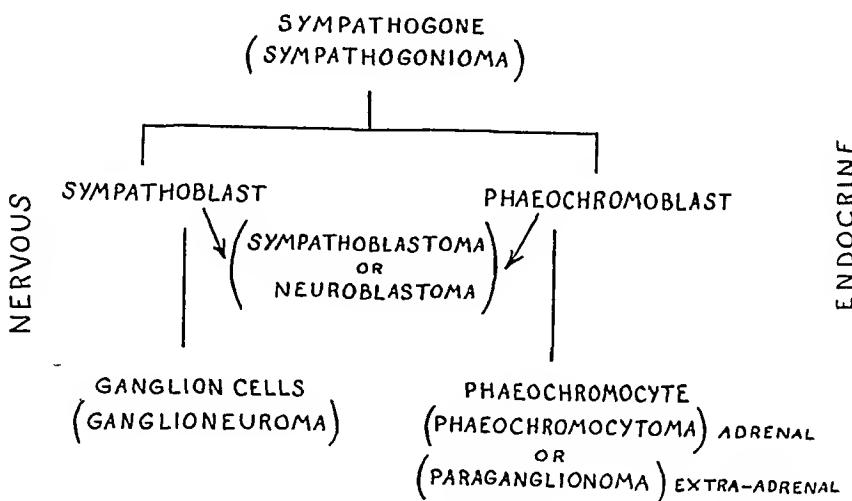


Chart I—Chart showing origins of adrenal medullary cells and tumors derived therefrom

function of the adrenal cortex There remain to be discussed those tumors which originate from the adrenal medulla Chart I indicates the differentiation of the cells of the adrenal medulla and the tumors that may arise at the various stages of development Of these tumors only those derived from the pheochromocytes have endocrine significance (Chart I)

The sympathogoniamata are a very malignant group of tumors that occur during intrauterine life or earliest infancy They are usually bilateral and result in early death They include many of the so-called retroperitoneal sarcomas and the round-cell sarcomas of infancy

The neuroblastomas are tumors that usually occur in childhood and present themselves clinically as retroperitoneal malignant growths In 1901 Pepper<sup>18</sup> reported one case and reviewed five others In 1907 Hutchinson<sup>19</sup> reported ten cases of adrenal "sarcoma" in children with metastatic deposits in the skull and orbits From a histological point of view the tumors described by Pepper and Hutchinson are identical, but there has persisted a clinical differentiation The Pepper type is characterized by the preponderance of abdominal signs, a large liver, ascites and cachexia The Hutchinson type presents tumors in the skull, especially about the orbits, with proptosis and ecchymosis of the eyelids, and may resemble chloroma or infantile scurvy

It has been suggested that the Pepper, or abdominal type, results

from a tumor of the right adrenal gland because of its intimate vascular and lymphatic connections with the liver, while the Hutchinson or osseous form of the tumor arises from a primary lesion of the left adrenal gland as a result of lymphatic drainage to the left intercostal vessels and through the deep cervical chain to the base of the skull. It is doubtful whether this schematic concept is adequate. These tumors are not associated with the sexual changes seen in cortical tumors and are without endocrine significance.

New growths derived from the mature pheochromocytocytes may occur in any location where pheochrome tissue exists. They have been reported as arising in the carotid body, the retroperitoneal tissues, along the abdominal aorta and its branches, the organ of Zuckerkandl, and in the sacrococcygeal region as well as in the adrenal medulla itself. The general clinical features are similar no matter where the tumor originates, and are due to the secretory activity of the growth. Large amounts of adrenalin have been isolated from such tumors. Belt and Powell<sup>9</sup> estimated 20 grams of adrenalin to be present in a growth weighing 1000 grams.

The patients are usually adults although the tumor has been reported as early as the second year of life, and as late as the eightieth. The growth is rarely bilateral, and may vary in size from several millimeters to 12.5 cm. in diameter.

The tumors are well encapsulated and often surrounded by a shell of normal adrenal medulla and cortex. They are prone to hemorrhage and necrosis with cystic changes. Microscopically, the tumors consist of nests or cords of polyhedral cells separated by their connective tissue stroma rich in capillaries. The predominating cellular element is a polyhedral cell with abundant finely granular cytoplasm, and a large nucleus containing a chromatic network. The affinity for the chrome stain is variable, some cells staining deeply and others lightly or not at all. Hyaline inclusions are present.

The characteristic clinical feature presented by these tumors is the occurrence of pirovsmal crises which may occur spontaneously or may be induced by emotion, exposure to cold, physical strain, manipulation of the tumor, or any of the pharmacological procedures known to cause adrenalin secretion. These crises resemble the symptoms produced by a large dose of adrenalin, namely, anxiety, pallor, tremor, sweating, nausea, vomiting, headache, cardiac palpitation, tachycardia,

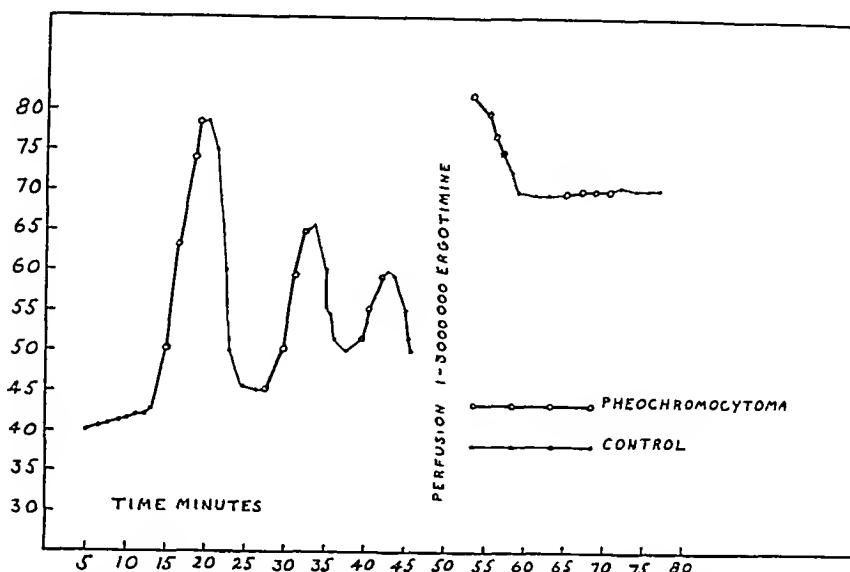


Chart II—Illustrating pressor effect of patient's plasma when perfused through denervated rabbit's ear and the reversal effect of ergotimine (From Beer, King and Prinzmetal)

a feeling of constriction in the chest, dyspnea, hyperglycemia, glycosuria and a sudden marked increase in blood pressure, particularly systolic. As a rule, the relative rise in the systolic blood pressure exceeds the rise in diastolic pressure but diastolic pressures of 240 mm of mercury have been reported. The paroxysms may be rare or may occur as frequently as every 30 minutes. In the early phases the blood pressure may be normal between attacks, but as the disease progresses, permanently high blood pressure with all of its cardiovascular concomitants is encountered. Death may occur in shock or pulmonary edema during a paroxysm, and sudden death has been reported after such trivial procedures as a tooth extraction, anesthesia or a minor operation.

Clinically the syndrome is frequently confused with exophthalmic goiter, and in several cases thyroidectomy has been performed. The association with thyroid adenoma and thyroid carcinoma has been recorded.

The final evidence for the hormonal nature of the symptoms, the demonstration of a hyper-adrenalinemia was long delayed. Earlier attempts are recorded, but I think that the first demonstration of the presence of an excess of adrenalin in the circulation during a paroxysm was made by Beer, King and Prinzmetal.<sup>21</sup> In 1937 they observed a

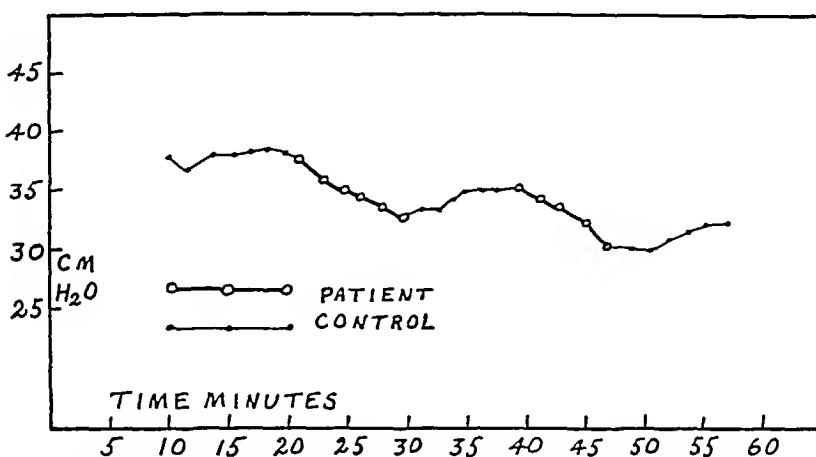


Chart III—Illustrating absence of pressor effect of patient's plasma following operative removal of tumor (From Beer, King and Prinzmetal)

patient with a pheochromocytoma in whom crises could be induced by exercise I show you two of their charts. The first shows the vasoconstrictor properties of the plasma and the disappearance of these properties after ergotamine. This is strong presumptive evidence of the presence of circulating adrenalin or at least an adrenalin-like substance. The second shows the absence of vasoconstrictor properties in the serum after the tumor had been removed (Charts II, III).

There have been presented this evening two interesting and important clinical states. One of these, due to a tumor of the pheochrome tissues, is quite clear-cut in its pathogenesis, clinical features and treatment. The other, Cushing's syndrome, is still in the process of being moulded into its final shape. Time will decide whether it is really a pituitary, adrenal or polyglandular syndrome. It is, at least, an interesting one.

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## SURGICAL CONSIDERATIONS IN THE TREATMENT OF CHRONIC LYMPHEDEMA AND OF VARICOSE VEINS\*

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**S**URGICAL procedures should be based on physiological and clinical understandings of the problems, and elucidation of these problems by such authorities as we have heard tonight, makes one realize how ineffectually we have been forced to grope surgically without adequate preparatory knowledge. Surgery's history is one of trial and error, and with such careful physiopathological research to guide us, our responsibility in the operative field of the future will be greater.

The lymphatic system is one of great surgical importance, because our triumvirate of tissue response, localization and absorption from infection are dependent upon its proper function, while our concept of surgery in malignancy rests on *en bloc* excision of the tumor and its primary extent to neighboring lymphatics. My discussion of the lymphatic system will be confined to that group which we consider amenable to modifications of the original Kondoleon principle, namely, the elephantiasis cases. Many of these patients with lymphedema, from an etiological standpoint, are not classifiable in the light of our present knowledge. In an effort to clarify them, we have prepared a surgical classification based on whether or not they might be expected to respond to surgical intervention.

### SURGICAL CLASSIFICATIONS OF LYMPHEDEMA

#### I Amenable to Surgical Treatment

##### 1 Modified Kondoleon Procedure (as presented)

###### a Idiopathic

###### 1 Præcox

###### 2 Congenital or familial (Milroys)

\* Read December 7 1939 at the Stated Meeting of The New York Academy of Medicine in the Symposium on Disorders of the Venous and Lymphatic Systems

- b Acquired
  - 1 Trauma (accidental or surgical)
  - 2 Filariasis Bancrofti
  - 3 Occasionally group secondary to venous pathology
- 2 Local Surgical Intervention
  - a Pressure, growth, etc
  - b Traumatic or operative scars
  - c Most venous obstructions
  - d Local inflammation
  - e X-ray, radium and other burns
  - f Congenital lymph collections (cystic hygroma, etc )

## II Not Recommended for Surgical Treatment

- 1 Milk idiopathic lymphedema
- 2 Fungus infections
- 3 Malignancies with invasion
- 4 Allergic or systemic lymphedemas

In a study of the last twenty-four patients diagnosed as having advanced lymphedema at the Vascular Clinic in New York Post-Graduate Hospital, eight have been the so-called simplex or *præcox* form, eight have followed chronic phlebitis—for the most part, after operation—five have been secondarily due to severe varicose venous pathology, two have been familial, or in the true Milroys group, one has been of filarial origin and two have followed infection—one after lymphangitis and one after epidermophytosis During the past year eleven patients with occlusion of the lymphatic channels have registered Two were post-infectious, one, post-traumatic, two, postoperative, and six were of the idiopathic type For the past three years selected patients from this last group have been subjected to a modification of the original Kondoleon procedure and this modification will be described in detail

The lymphatic system, being a separate and complete circulatory system of itself, resembles the venous system and picks up such tissue products as the venous system does not remove In lymphedema, an occlusion occurs in the lymphatic vessels, which may be caused by pressure, inflammation or thrombosis Fibrosis soon follows and the drainage of these lymphatic vessels is permanently closed, possibly accelerated by the increased protein content, which Drinker, Field and

Homans found to reach a height of 4 per cent Lymph then accumulates in the tissue spaces, with no normal method of escape With elevation of the part, it passes through the tissue spaces to the abdomen and is drained With dependency, it again collects and with increasing distension the size of the part increases

In mild cases of lymphedema, mere support is sufficient, the wearing of a rubber stocking and elevation of the leg for part of the day, with a restricted activity, permits these patients to continue quite satisfactorily In certain patients, mecholyl by iontophoresis has relieved mild lymphedema and Irving Wright, of the Vascular Clinic, has a followed series of these patients In others, however, supportive measures are entirely inadequate and in general the results have not been too encouraging In progressive cases the part becomes so large that it is unwieldy and disfiguring, and with periodic febrile reaction, many of these individuals become economic liabilities Some present themselves requesting amputation

While the early conception of skin lymphatic drainage through muscles as suggested by Handley and Kondoleon is partly erroneous, and some of the beneficial results depend on excision of large sections of lymph accumulations in subcutaneous tissues, it appears that after the operation some of the lymph may be eliminated through the muscles If this were not true, the local excisions of Dieffenbach and Mikulicz would have been more successful Recent biopsies on our patients six and eighteen months after operation showed a normal histological arrangement of the fat cells and no lymph collections If the therapeutic effect depended on local excision only, some lymph collections should be present in one and a half years

Regardless of the manner in which the surgical removal of the subcutaneous tissue and fascia acts physiologically, it is a means of affording relief in a high percentage of patients Preoperative and postoperative measurements in five extremities, which we have carefully watched for from six months to two years, have shown and maintained a reduction in the circumference of the leg from a minimum of seven inches in one patient, to a maximum of twenty-one and one-eighth inches in our most advanced case All of these patients have had a one stage procedure, which can be briefly outlined as follows

The patient is hospitalized, with the leg elevated, for two weeks, during which time diuretics are administered The frequently accom-

panying fungus infection is cleared and sulfanilamide is given. This drug has been used somewhat empirically. Drinker and Fields showed in their work in experimental elephantiasis in dogs, that just as the febrile reaction occurs, there are streptococci present in the lymph and it is to eliminate these organisms that the sulfanilamide is given.\*

We would emphasize the careful selection of the patient, the pre-operative preparation, spinal anesthesia, measuring of the size of the leg, the undermining of at least three-fourths of the circumference, care at the joint, the use of alloy steel wire to reduce reaction and blood transfusion. By being sufficiently radical we have been able thus far to eliminate a second stage operation on the medial side of the leg. In only one instance have we had any slough and that was over the dorsum of the foot, where we tried considerable undermining. In this patient, we were operating on a recurrent lymphedema and the previous scars were a factor. Incidentally, the deep fascia had entirely regrown since a previous, much less radical operation at another institution five years before

#### SURGICAL TREATMENT OF VARICOSE VEINS

While surgical eradication of Venous Pathology is at present much more advanced than that of the lymphatic system, we must admit to an even longer misunderstanding of the physiological problems on which our operations must be based. The consideration of all of the ramifications of the venous system, of course, is impossible, so I will confine my discussion to that of the varicose vein problem. The pendulum of conservative or radical therapy has swung back and forth somewhat more rapidly in the treatment of varicose veins than in other problems. Surgical history illustrates again that there is little new that one can do,

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\* A short motion picture was presented demonstrating the operation. This detailed a surgical technique consisting of an incision starting over the greater trochanter on the lateral aspect of the leg and continuing to the external malleolus, with an elliptical excision of skin sufficient to make the remaining circumference equal the unaffected leg. This incision was brought together at the knee to prevent joint constriction. A dissection of the skin flaps was then made until 75 per cent of the circumference of the skin of the leg had been raised from the fat layer. No transverse incision was employed. The incision was then continued through the fat and deep fascia layers and the skin, superficial and deep fascia were removed en masse, permitting the undermined skin to fall on the denuded muscle. After hemostasis was secured, the skin was closed with interrupted #32 and #36 alloy steel wire without drainage. Blood transfusion was performed and the limb was encased in supporting bandages. The patient was shown immediately and three months after the operation. Other patients were also presented by the motion picture, both before and after the operation.

except to better apply the understanding we have of physiological and pathological processes Hippocrates ligated the saphenous vein and injections for varicose veins were performed the same year the syringe was invented Our only improvement is in asepsis, surgical technique and the proper location of the ligation points

To understand the varicose vein problem, the anatomy and physiology of the venous return from the leg must be briefly recalled The venous return depends on a deep femoral and a superficial greater and lesser saphenous system These deep veins are well supported and protected by muscle and adequately valved, while the saphenous veins are subcutaneous, subject to trauma and without muscle protection or support The great saphenous vein, the one involved most commonly in varicose veins, drains the medial aspect of the leg and empties into the femoral vein at the fossa ovale Reflux blood from the femoral vein normally is prevented from entering the saphenous vein by the saphenous-femoral valve and inadequacy of this valve permits femoral vein blood to flow reversely into the saphenous vein, with back pressure, further valve incompetence and varicose veins The area on the medial aspect of the leg is inadequately drained, constantly bathed in stagnant, deoxygenated blood and the result is edema, discoloration, dermatitis and frequently ulceration The two venous systems intercommunicate at other points and if the valves fail in these communicating branches, there will be reflux blood at these points also, the so-called "blow-out points" The lesser saphenous vein, draining the posterior aspect of the leg, empties into the popliteal vein It may be involved in the process

After a thorough survey of the patient has been completed, and a study of the arterial supply made, our problem with these patients is then to determine

- 1 If the deep veins are open and adequate This can be done simply by a modification of the Perthes test
- 2 If the saphenous-femoral valve is incompetent, the Trendelenburg test shows this satisfactorily
- 3 Incompetence of the valves of the communicating branches must be demonstrated and a very simple test, which we have devised in the Vascular Clinic has proven satisfactory to us This is done by elevating the leg to empty the veins, applying a tourniquet below the fossa ovale to prevent saphenous-femoral reflux, and applying an Ace bandage from the toes to the tourniquet With the patient

standing, the Ace bandage is removed from above down and any "blow-out," as it appears, is marked and measured from the lower tip of the patella

#### 4 Incompetency of the lesser saphenous must be recorded

We now have completed the third year of a five year study, using the technique\* outlined and our results, while too early to be conclusive, are very encouraging. There have been no deaths and no occurrence of anaphylactic shock. In four instances there have been allergic symptoms, manifested by febrile reaction, urticaria and local redness. In three patients there have been local sloughs, due we believe, to technical failure to apply pressure at an area of redness, indicating sclerosing solution collection. The catheter has been introduced on an average of 37.4 centimeters in the last one hundred cases and 26.2 cc has been the average amount of injection. Of the patients who have been followed for over one and one-half years, we have had fifty-one entirely satisfactory, two partially satisfactory and two unsatisfactory.

The two partially satisfactory patients have been ones in which there was a plexus of branches at the fossa ovale requiring ligation only and

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#### \*SYNOPSIS OF MOTION PICTURE PRESENTED TO ILLUSTRATE THE DESCRIBED TECHNIQUE

After infiltration with local anesthesia at the fossa ovale, the saphenous vein, together with its branches, was dissected free. After ligating and dividing the branches, the saphenous vein was resected at its femoral junction, the proximal end being transfixed and ligated. Through the open, distal end a ureteral type catheter was inserted for a distance of 50 cm and a sclerosing solution (3½ per cent sodium ricinolate) was injected, as the catheter was withdrawn.

The advantage of the catheter method was illustrated by sections of the veins of experimental animals which showed that the sclerotic effect from any injection solution is localized and to sclerose a large vein the solution must be uniformly and segmentally distributed.

The distal end was then resected for two inches and transfixed and ligated. The wound was closed without drainage. A secondary incompetent communicating branch or "blow-out" just below the knee was resected and ligated. The patient was then made to walk around the operating room and a supporting bandage was applied from the toes to the knee. Accumulations of sclerosing solution were prevented by pressure pads. As much as 10 to 50 cc of the solution was the amount advocated for sclerosis.

While the amount of solution mentioned may sound radical to some, the reaction is so spaced throughout the vein course that local deleterious effects are unusual. A suggestion that the solution might enter the deep femoral system and cause sclerosis is more theoretical than actual. We have seen no evidence that this occurs in more than one hundred and fifty injections performed with this technique. We know that sclerosing solutions in the form of 50 per cent glucose, are injected daily in competent veins without ill effect and the use of the moving catheter restricts the amount of the solution that would run into the deep vein at any one point.

later injection at the clinic. We have not had as satisfactory results when the injection is performed secondarily, due we believe, to inadequate saphenous sclerosis in the thigh, where local injections are often difficult. The two unsatisfactory patients both had chronic phlebitis and probably incompetent communicating branches, masked by the chronic edema. The postphlebitic group definitely are more difficult to treat. The sloughs were approximately the size of a silver quarter. These slowly granulated, requiring about six to eight weeks. The only slough that has occurred since the postoperative routine inspection was established, was at the Welfare Hospital in an elderly, bed-ridden individual.

#### IMPROVEMENT OF ARTERIAL CIRCULATION BY SAPHENOUS VEIN SCLEROSIS

Restricted arterial circulation always has been a contraindication to varicose vein injection and Homans has stated that a thrombosis in a vein may cause an arterial spasm, which may result in gangrene. We had noticed a decrease in the oscillometric readings in all of our varicose vein patients after ligation and retrograde sclerosis, which indicated that less arterial pressure was necessary for circulation after the inadequate veins were eliminated. In studying the physiology of the capillary system, it seemed to us that some of these patients with deficient arterial supply would have their arterial circulation improved if the peripheral resistance could be reduced. The capillary system is part of the peripheral resistance and is a closed system—the blood actually coming in contact with tissue cells in only two organs, the liver and the spleen. Taking the data of Landis as a criterion for discussion, the pressure in the arterial end of the capillary loop is approximately 32 mm mercury. The osmotic pressure in this area is twenty-five, thus giving an outward driving force at the arterial end of plus seven. At the venous end of the capillary the intracapillary, or outward force pressure, has fallen to twelve, which is below that of the osmotic pressure, which is slightly increased, due to concentration, thus normally permitting an equal absorption from the tissue spaces at the venous end. In the presence of varicose veins, with obstructed venous outflow, the pressure at the venous end of the capillary increases and may rise higher than that of the arterial end. Beecher lately has shown that there is an increase in the positive pressure in the saphenous vein in varicose veins which averages 50 cm of water in excess of colloidal pressure. Thus in varicose veins, the normal re-

absorption of tissue fluid at the venous end is impossible and tissue fluid must be carried off by the lymphatic system, if at all. An increased capillary and peripheral resistance follows, thus making the blood supply through arteries already damaged, more difficult. Elimination of varicose veins, if safely accomplished, should be expected to improve the arterial circulation. In a group of patients suffering from advanced occlusive vascular disease—six with advanced arteriosclerosis and three with thromboangiitis obliterans—accompanying varicose veins have been eliminated by the procedure already mentioned and clinically all but one patient has been improved. Claudication has decreased, oscillometric readings have been lowered, thus indicating the necessity of less artery pressure. In one instance, a trophic ulcer quite promptly has healed. In the one unsatisfactory result, a major amputation, unrelated to this procedure, was necessary one year later. Further investigation along this line is being done at this time. Care is necessary to prevent accompanying arterial spasm by using a small amount of solution, closely watching the postoperative course and at times, using antispasmodics.

The history of varicose vein therapy has shown us that it is difficult to say that any specific procedure is satisfactory until many years of observation have passed. We do think, however, that our present line of attack is physiologically and anatomically more sound and we hope that our subsequent follow-ups will bear this out.

## MECHANISM OF ALLERGY\*

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THE TERM allergy is applied to a variety of conditions based on different forms of specific hypersensitivity. In the present communication, discussion will be limited to the mechanism operative in that group of allergic diseases known as the atopic illnesses. In this category, hay fever and asthma are the outstanding examples, although certain forms of infantile eczema, urticaria, angioneurotic edema, and other food and drug sensitivities may also be included.

The term atopy is applied to the above mentioned clinical conditions on the principle that they are all hereditary in nature. The hereditary factor manifests itself in its influence upon the number of offspring affected and upon the age of onset of the illness. To a lesser degree, the particular form of atopy which develops, as well as the nature of the sensitivity, is affected by the hereditary influence.

The mechanism of anaphylactic shock, which, by definition, involves the participation of precipitin anchored in a shock tissue of smooth muscle, has not been found operative in atopic reactions.

The typical atopic reaction is ordinarily described as that resulting from the union in certain predisposed tissue cells or shock tissues, of an excitant or allergen with a peculiar antibody known as the atopic reagin. This antigen-antibody reaction occurring on or within the cells, according to the theory of Lewis and Dale, results in the liberation of histamine or a substance of a similar nature which produces an increased vascular permeability. The resulting edema is the most important factor in the production of clinical atopic symptoms.

The allergen-reagin reaction seems not to be the sole means by which the atopic shock tissues may be stimulated. The same result may be effected by mechanisms in which neither reagins nor any other antibodies can be demonstrated. There is reason to believe that, under cer-

\* Read February 1, 1940 at the Stated Meeting of The New York Academy of Medicine in the Symposium on Allergy.

tain circumstances, the shock tissue may even be stimulated non-specifically

The atopic reagin is the peculiar human antibody which mediates the positive cutaneous reactions elicited by skin tests with various allergens in the diagnosis of atopic illnesses. Although primarily a circulating antibody, it manifests a definite affinity for various tissues. Its affinity for the skin is demonstrated by the ease with which any normal human skin can be passively sensitized by an intracutaneous injection of a reagin-bearing serum. In a series of studies in mucous membrane hypersensitivity, Sherman and Gray and their co-workers have shown that the human ophthalmic, nasal and intestinal mucous membranes can be sensitized as easily as the skin by intramucosal injections of reaginic sera. In fact, when skin and mucous membrane were locally sensitized with injections of the same serum and the related antigen was administered either orally or parenterally, the reaction at the site in the mucous membrane usually preceded that at the cutaneous site by several minutes. Evidence of the affinity of the atopic reagin for placental tissue is found in the fact that Bell and Eriksson and all subsequent investigators have never found maternal atopic reagins in the fetal circulation, although other maternal antibodies regularly pass through the placenta. Even when he actively induced sensitization during pregnancy with the antigen of *Ascaris lumbricoides*, Zohn could not detect any of the maternal atopic reagins for this antigen in the cord blood at birth. It is undoubtedly this affinity of the reagins for the placental tissue which renders the passive intrauterine sensitization of the human fetus highly improbable.

The affinity of the atopic reagin for animal tissues had not been satisfactorily demonstrated until the recent experiments of Caulfeild and Straus definitely established the possibility of sensitizing the skin of the Rhesus monkey with these antibodies. Further studies by Straus and his co-workers demonstrated the ability of the human atopic reagin to sensitize the stomach, intestines, gall bladder and spleen of the Rhesus monkey. The peritoneum could likewise be passively sensitized, giving experimental basis for the belief that serous surfaces in humans may also participate in atopic reactions. Attempts at passive sensitization with the atopic reagin in laboratory animals other than the monkey have thus far proved unsatisfactory.

The question as to whether atopic reagins can be produced by

experimental animals is not yet answered. However, the results of recent experiments on guinea pigs and rabbits by Sherman, Stull and Hampton, by Caulfeild and by Eagle and their co-workers support the earliest contentions of Cooke and Spain that certain immune rabbit sera can passively sensitize some human skins. Because of the irregularity with which such sensitization is accomplished with each serum, and because of the atypical nature of the reaction resulting from testing the sensitized sites, it is not yet clear whether these unusual skin-sensitizing antibodies are the same as the atopic reagins. This question needs further investigation.

In contrast to the relatively strong attraction existing between the precipitin and its antigen in anaphylactic sensitivity, the reagin and its specifically related allergen are only loosely bound to each other. The affinity of the reagins for the tissue cells is much stronger than that for its antigen. Hence, reagins may sensitize the human skin cells even in the presence of antigen.

A mistaken impression commonly held is that the atopic reagin is the sole criterion for the diagnosis of atopy. There are certain types of antigens, however, such as *Ascaris lumbricoides*, *Trichinella spiralis*, horse serum, insulin, and liver extract which stimulate reagin production equally well in non-atopic and atopic individuals. On the other hand, there are some forms of atopy in which reagins are absent and in which even the involvement of an immunologic mechanism may be questioned. It is obvious, therefore, that the heredity of a predisposed shock tissue is much more fundamental in the concept of atopy than is an immunologic mechanism involving a hypersensitivity.

Unlike laboratory animals in anaphylaxis, man has no characteristic atopic shock organ. One is even at a loss to designate the shock tissue in which the atopic reaction takes place, although many observers consider the reaction primarily a vascular one. However, the smooth muscle, which is acknowledged to be the primary shock tissue in anaphylaxis, has now been ruled out as a possible atopic shock tissue by most investigators. Failure to sensitize the guinea pig smooth muscle with human reagins was consistently obtained by Coca and Grove and by subsequent workers, while recent experiments have yielded evidence in the same direction which is even more convincing. Although the skin and mucous membranes of the Rhesus monkey can be easily sensitized with small amounts of human reaginic sera, Albert, using the Dale technique,

could demonstrate no fixation of reagins in the smooth muscle of the monkey's intestinal strip even though excessive amounts of potent reaginic sera were used for sensitization. Using a human uterine muscle segment obtained from a patient with a positive cutaneous reaction and with circulating reagins for horse serum, Tuft also failed to elicit specific contractions with the Dale technique. Approaching the problem from a different angle, Feldman and Sherman, by means of the slit lamp, studied the responses of naturally and passively sensitized human conjunctivae to excitation with the specifically offending allergens. No evidence of vascular contraction was detected at any time during the allergic reactions. There exists, therefore, no experimental justification for the assertion frequently made by the clinician that, in bronchial asthma and in gastrointestinal allergy, the smooth muscle is the primary seat of the allergic reaction.

Evidence recently obtained also tends to exclude the epithelial lining of the mucous membranes as the seat of the allergic reaction. Of interest in this connection have been Grayzel's observations in microscopic studies of the allergic reactions in the organs of the Rhesus monkey passively sensitized with human reaginic sera. In the gall bladder and intestines, the blood vessels and the connective tissue of the lamina propria and submucosa seemed to be most affected while the epithelial cells and muscle cells appeared least involved. Marked edema of the loose tissues, engorgement of the vessels, and infiltration of the connective tissues with cells, frequently perivascular in distribution, were findings common to all specimens.

There is additional experimental evidence to indicate that the seat of the atopic reaction is not in the epithelial layers of the sensitive mucosa. Sherman and Kaplan reported that topical applications of the specific excitant to the passively sensitized nasal mucous membrane in humans was far less effective in inducing an allergic reaction than an intramucosal or parenteral injection. Similarly, Gray found that, in the passively sensitized human rectal mucous membrane, the local application of the specific excitant to the sensitized site did not, as a rule, produce a maximal allergic response. The reaction seemed to reach its height only after the excitant had been absorbed into the circulation, the occurrence of the latter being marked by the spontaneous lighting up of a cutaneous site sensitized with the same reaginic serum. Hence, the passively sensitized mucous membrane sites seemed to receive a weaker excitation from

local contact with the antigen than from its absorption, through the mucous membrane, into the circulation and its contact with the shock tissues from within. The fact that this can occur renders it unlikely that the epithelial cells which line mucous membranes are the ones most involved in the atopic mechanism.

The hypothesis that the increased vascular permeability in the allergic reaction results from the liberation of histamine or a histamine-like substance does not appear to be entirely adequate. Abrahamson by iontophoretic methods could not detect the presence of histamine in allergic wheals. Bowman, in clinical studies, showed that a reaginic reaction in the naturally sensitive skin increases the capillary permeability at that site upon subsequent stimulation, while a histamine reaction produces the opposite effect. The allergist finds confirmation of an increased vascular permeability following atopic reactions in the fact that, after a constitutional reaction resulting from pollen therapy, the patient's tolerance to dosage is definitely diminished. Despite these weaknesses in the histamine hypothesis, a more satisfactory theory is not yet available.

There are still many who believe that sensitization to foods and inhalants is an accidental phenomenon based on the degree and interval of exposure to these allergens. That adequate antigenic stimulation is necessary for the development of hypersensitivity is generally agreed, as is also the fact that the absorption of traces of ingested and inhaled antigen into the circulation in an unaltered form is a normal and physiologic phenomenon which facilitates sensitization to all of these allergens. The recent studies of Harten and Bowman, however, have yielded convincing evidence that, in atopic individuals, the hereditary predisposition to become sensitive to certain antigenic groups plays an important role in the sensitivities which are developed. It was found that of 500 patients with frank pollinosis residing in this city, all of them, with only six exceptions, showed positive cutaneous reactions of varying degree to representatives of all of four groups of ubiquitous pollen, namely, timothy, ragweed, plantain and trees. For the latter test a mixture of six common tree pollens was used. These positive reactions were specific, as they were transferable to normal skins in more than 97 per cent of trials. In 100 atopic cases with no frank hay fever symptoms, uniformly negative reactions to all of the four pollen groups occurred in 37 per cent and uniformly positive ones in 55 per cent. In 8 per cent

there was an absence of uniformity. Two sera obtained from hay fever cases in Hawaii, where the pollinating flora is different from ours, showed a lack of uniformity when tested for the presence of reagins for the aforementioned four pollen groups. Since there is no evidence of a common antigen in these pollens, the findings point strongly to a predisposition in pollinosis cases to sensitization to the pollen antigens. The preponderant uniformity in the co-existence or absence of such sensitivities excludes degree and interval of exposure as significant factors in their development. The conclusion seems justified that the element of accidental or unusual exposure to common allergens is of much less importance in inducing atopic hypersensitivity to these substances than is generally assumed to be the case.

## ALLERGY IN CHILDHOOD\*

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**T**HE earliest common clinical manifestation of allergy is eczema. The eczema problem is made difficult by the fact that under this heading are grouped several dermatoses which are unrelated etiologically, but which may be similar in appearance. However, it is probably true that at least 75 per cent of eczematous infants are allergic.

The first allergen to which most of them become hypersensitive is egg white, although they have never eaten it. Whether the sensitization is hereditary, congenital, or by transmission of antigen through the breast milk, need not concern us here—the important practical fact is that the baby is either born sensitized, or is sensitized in the first few weeks of life. Although egg white is the most common allergen concerned in hypersensitivity when the baby has never eaten the food in question, the same thing may occasionally happen with other allergens, notably fish and nuts. This congenital or possibly hereditary sensitivity is usually of high degree; the baby is likely to be made violently ill if he eats even the smallest amount of his allergen. Although such sensitivities often occur in infants with eczema, they presumably are not directly concerned in its causation, for the sensitization is usually of such quality that the infant can take none of the food. Those sensitizations which cause eczema are milder, and to allergens to which there is continuous or frequent exposure without violent symptoms.

The most important allergen with which the young infant, already usually sensitized to egg white, next comes in contact, is cow's milk. He takes the same amount of milk protein regularly day after day and with modern methods of feeding in excessive quantities, as a rule over twice as much as if he were breast fed. He has been taking also orange juice, and soon begins with cereals and various vegetables. He may become sensitized to any of them. Many normal infants will for a short time give positive intracutaneous skin tests and have antibodies.

\* Presented February 1, 1940 at the Stated Meeting of The New York Academy of Medicine in the Symposium on Allergy.

in the blood after the introduction of a new food into the diet. The eczematous infant prolongs and exaggerates this normal immunologic response, and while he is doing so, he has eczema. Although it is by no means true that all such infants are sensitized to milk, and while sometimes other foods may be of more moment, it has seemed to me that this is by far the most important allergen in early life, and the one to which attention should be chiefly directed in any study of the immunology of infantile eczema. In a series of 153 infants under one year of age, with all sorts of eczema, allergic or non-allergic, 17 per cent gave positive scratch tests to milk. In another series of sixty-four, all with negative scratch tests, 56 per cent gave positive intracutaneous tests. Normal infants who have been taking milk for a considerable time, as did all these infants, do not react to it, so such positive tests are abnormal. Their etiologic significance, however, is quite another matter, and not all positive intracutaneous tests are etiologic. However, if the scratch test to milk is positive, it has been my experience that the eczema is almost always due to milk. The same holds true for wheat and other foods.

Of the two chief milk proteins, casein and lactalbumin, lactalbumin is by far of most consequence. It has been said that casein was of no significance as an allergen. I think, however, that Dr. Pratt and I have been able to show, in work soon to be published, that sensitivity to casein is not uncommon in infantile eczema.

Sensitization to the environmental allergens is not so frequent in early life as later, but can by no means be ignored. Many eczematous infants are at an early age sensitized to house dust and feathers, two allergens to which they are constantly exposed. There is no reason for believing that these are not of etiologic significance, but it is hard to prove that they are. Sensitization to other environmental allergens is only occasional during the first year.

Infantile eczema usually develops on an allergic soil, and what has been learned about allergy in the last few years has given at least a rudimentary understanding of eczema. Dietetic treatment, however, has been wrongly used so frequently in eczemas that have nothing to do with the diet, that dermatologists in particular, and sometimes rightly, have become skeptical of any but local treatment. However, there can be no doubt that the present conception of immunologic treatment, that is, removal from the diet or environment of those aller-

gens to which hypersensitivity exists, represents a real advance, even though there are many difficulties and inconsistencies attached to this conception, and even though it does not entirely explain eczema

It is not difficult to plan a diet for an allergic infant, with the exception of milk hence I shall not discuss the other foods The common practice of trying this milk and that, dried milks, patent foods, and various sugars, does no good

There are three methods of handling the milk situation that may do some good

- 1) The use of heated milk (usually evaporated)
- 2) Goat's milk
- 3) A milk free food

It has been my experience that in eczema heated milk is not often of value The reason for this is probably that while the antigenicity of lactalbumin is changed somewhat by heating, it may not be changed enough, and that casein is not changed at all, so that if casein sensitivity is present, there is no reason why heating should do good I have many times seen eczema due to milk sensitivity cured with a milk-free food, only to recur when evaporated milk was resumed, and cured again when it was omitted In spite of these objections it is probably the best form of milk if any cow's milk is used

With goat's milk results may be occasionally very satisfactory, more often no better than with cow's milk Goat casein is immunologically the same as cow casein, and in thirty infants who gave positive skin tests to cow casein, also tested with goat casein, there were identical reactions to both in every case It has been commonly said that goat and cow lactalbumin were species specific, but there has been no original work done upon which to base this assumption, except that by Versell in 1915, who found only that goat and cow lactalbumin were more species specific than goat and cow casein, but by no means entirely so We tested forty-four eczematous infants who gave positive reactions to cow lactalbumin with goat lactalbumin of the same strength There were ten entirely negative reactions to goat lactalbumin, nine doubtful reactions, much smaller than those to cow lactalbumin, and twenty-five identical positive reactions to both It is well known that some proteins contain two or possibly more antigenic determinants, one species specific, and one common to the protein in question and to other closely related proteins as well, and that an individual may

become sensitized to only one or to both of these determinants. Such seems to be the case with eczematous infants.

So milk sensitivity in eczema is in reality more complicated than appears on the surface. Some infants are sensitized only to the species specific factor of cow lactalbumin, others to the factor common to both cow and goat lactalbumin, and in either of these two groups there may be sensitization to casein as well. In still a third, but much smaller group, there may be sensitization to casein alone. It is probably due to this situation that goat's milk is not more often effective in dietetic treatment.

The ideal diet for any milk sensitive infant, provided he can digest it and thrive on it, is a food which contains no milk. With this in mind, we developed some ten years ago such a food, the basis of which is soy bean flour, and since then several other similar preparations have appeared. It has been our experience that better results are obtained with these foods than with any form of milk. If the eczema is caused by milk, it will be cured with a milk free diet, if it is not, such a diet is no better than milk. However, the soy bean foods have the disadvantage that they sometimes cause loose bowel movements and irritated buttocks. This is probably due to some property of the soy bean flour. We have found, however, that by boiling in a double boiler for three-quarters of an hour, this property is considerably lessened. We have had opportunity to feed many milk sensitive eczematous infants on such a milk-free diet, and consider it a valuable adjunct.

However, it is surely not wise to use a milk-free food as a routine. If the eczema is mild, whether or not skin tests to milk are positive, it can be very well controlled with local treatment, and it is unwise to make such a radical change in feeding. If skin tests have not been done, the use of such a diet is not the careful practice of medicine. The eczema may not be due to milk. In very young or in poorly nourished infants the risk of a digestive upset is too great. In erythroderma, where there is diffuse redness and scaling all over the body, blue feet, and a general glandular enlargement, a milk-free diet is not likely to do much good, in spite of the fact that these babies are strongly allergic and often give positive tests to milk. With these reservations, the milk-free foods are valuable in the dietetic treatment of selected cases of infantile eczema. They are by no means a cure-all, for there are many other causes of eczema which have nothing to do with milk.

The food sensitivities represent often a transient phase of abnormal immunology through which the infant may pass in a few months, and many tend towards recovery during the second year. At this time they can often take with impunity some of the foods to which they were previously clinically sensitive, although their skin tests may persist. However, some may retain their clinical sensitivity to certain foods for many years. According to Moro about 6 per cent continue with eczema all during childhood and even into adult life. At this period sensitivity to environmental allergens becomes more frequent.

In the treatment of infantile eczema the immunologic approach is not the whole story by any means. Skilled local treatment is many times of equal or greater importance, but inasmuch as the subject is allergy, I have stressed the allergic phase more than is justified.

It has become popular to say that many bottle-fed infants who suffer from malnutrition, vomiting, colic, diarrhea, and pylorospasm, are allergic to cow's milk. Some of this must be true, for so many people have said it, but I have seen but a few of these cases myself, and while I quite agree that sometimes some of these symptoms may be caused by allergy, I do not believe that they are commonly so caused.

There is another and very definite type of milk-allergy in early infancy that of the breast fed baby who goes into shock and collapse, always with vomiting, and often with diarrhea, when he first takes even the smallest amount of cow's milk, so that it is obvious that he cannot be fed it. There have been reported in the literature four deaths from the ingestion of small amounts of milk. These babies are not likely to have eczema, and scratch tests to milk are usually, but not always, negative.

In contrast to those with eczema, almost all of this group can take goat's milk without symptoms. I have seen only five babies of this type in 24 years, but have been able to collect fairly accurate data of twenty others from the literature and from personal communications. Of the twenty-five, goat's milk was tried in sixteen, and was tolerated in every instance. The sensitization here is apparently clean-cut and sharp to the species specific factor of cow lactalbumin alone. It seems likely that the immunology of these infants is somewhat different than in those with eczema, although there are scarcely any data available. In the blood serum of the only one that I have been able to examine, reagins to cow's milk were absent, although shock was quickly pro-

duced by the taking of only a few drops of milk. The time conditions of antigenic exposure are quite different than in those with eczema, which possibly accounts for the clinical and immunologic differences.

The eczematous infants are taking large amounts of milk each day, and thrive except for the eczema. They are continually exposed to their allergen, and have become mildly sensitized, and perhaps partially immunized. The shock cases, on the other hand, have never come into contact with cow's milk except possibly in utero or during the neonatal period. When they are exposed to it again at the time of weaning, after a long period of abstinence, they react so violently that it is quite impossible for them to be raised on it. The situation here seems more closely analogous to animal anaphylaxis, and suggests in a striking manner the variations in degree and type of sensitization that may be brought about possibly by differences in the time interval and frequency of exposures. This seems to me of fundamental importance in any consideration of the mechanism of sensitization.

There are admitted frequently to the wards of every large children's service, children between the ages of 4 and 12 years, who have recurrent attacks of abdominal pain. These children are studied to rule out the possibility of tubercular abdominal lymph nodes, chronic appendicitis (if there is such a thing), pyelitis, kidney stone, or various anatomical anomalies of the digestive tract. It is not common to find a cause for the attacks of pain, and they are often discharged without any diagnosis having been made, and are lost track of. Some of these children have food allergy, but I think that such a diagnosis should be made with extreme caution and only after every other possibility has been excluded. Furthermore, unless the pain comes at frequent intervals, or unless the history points to some definite food, it is not satisfactory to study the possibility of food allergy while they are in the hospital, it takes too long. Skin tests are often negative, and it is in this type of patient that elimination diets may be of value. I do not like complicated systems of elimination diets, one gets tangled up in them. It has seemed to me better to put the child on a very simple diet containing only a few foods which rarely cause allergic symptoms, and which have given negative intracutaneous skin tests. If the pain is not relieved, the attack was probably not due to allergy, if it is relieved, suspected foods are added one at a time and results noted. I have seen a very few children in whom such attacks of pain were of allergic

origin The child with asthma or eczema who has violent gastrointestinal symptoms if he eats food to which he is already known to be sensitive, is in a different category, and offers no diagnostic difficulty

I cannot believe that recurrent or cyclic vomiting is commonly caused by allergy there is too much evidence that it is primarily a metabolic disorder The occurrence of acetone in the urine often before the vomiting begins, the often low blood sugar, the prompt cure by the intravenous injection of glucose and insulin, and the fact that it may be produced artificially in susceptible children by a ketogenic diet —all indicate its metabolic origin although it is, to be sure, but imperfectly understood

The paralysis which may occur after the administration of tetanus antitoxin is witness to the fact that allergy may affect the nervous system, and, as Foster Kennedy pointed out in an admirable address here last year, the essential lesion of allergy is edema, and if there is edema in or around nerve tissue the function of that tissue will be disturbed There can be no doubt that some cases of migraine are allergic in origin, although in my experience this disorder is not common in children However, I have seen recently one boy entirely cured of a long-standing and severe hereditary migraine by the omission of wheat, chocolate and celery from the diet

In short, there is a miscellaneous group of somewhat obscure conditions in which food allergy may be sometimes operative, but I am afraid that some of the more progressive allergists may have made too much progress in some of these matters I think the more conservative ones would agree that the diagnosis of food allergy in such conditions should be made only with great caution, and only when the evidence is incontrovertible there are too many other causes for such symptoms, particularly in the digestive tract In the selected material of the allergist, food allergy may be common in unselected material it is not If allergy is to keep a good reputation, it must not claim too much, and must tread softly and speak modestly when dealing with this borderline group

Respiratory allergy is not so common in early infancy as in later infancy and childhood, but even young infants may have asthma or vasomotor rhinitis Also, there is a growing belief that the so-called capillary bronchitis of young infants, which has always been so amenable to adrenalin, may be allergic The child with frequent colds,

particularly if they occur all the year round, may be suffering from allergic rhinitis, and such a possibility is worth investigating. However, I have the impression that the allergic child is more susceptible to ordinary infectious colds than is the normal child.

Asthma is to the older child what eczema is to the infant. The chief differences between asthma in the child and in the adult are that a higher proportion of cases in children is allergic, and that, while respiratory infection is important as a co-existing or predisposing factor, it is not so important as in the adult asthmatic of long standing, with his chronic bronchitis, emphysema, and permanently deformed chest. The greater the chronic infection, the greater the permanent damage, the worse the prognosis. The prognosis as to relief or even cure is therefore better in the child than in the adult.

While food allergy may play a part in asthma, environmental allergens are, as a rule, more important. I think most allergists would agree that many positive skin tests to foods in older children are simply residues of past clinical sensitivities, without significance, for it is common for a skin test to persist for a considerable time after the clinical sensitivity has been lost. Furthermore, some positive skin tests may never have been of etiologic significance. It is usually a mistake to omit a large number of foods from the diet of an older asthmatic child, no matter what the skin tests show. One finds occasionally, but all too rarely, an asthma that is due to one definite allergen and one alone. More often the sensitivity is multiple, and a strongly allergic child may give many positive tests to foods and inhalants, which represent all degrees of clinical sensitivity. Some food proteins which previously passed unsplit through the intestinal mucosa, do so no longer. Some which caused symptoms at one year do not at five years, even if unchanged protein is absorbed. Others may still be in the acutely hypersensitive phase. The allergic child is never static, his allergic pattern is continuously changing, he is becoming acclimated to some allergens and sensitized to others.

It is not easy to determine which skin tests are of clinical significance, and no allergic individual can be dealt with correctly solely on the basis of his skin tests. The only real criterion is production of symptoms on exposure to the allergen. This requires careful history taking, accurate clinical observation, common sense, and the ability to evaluate the relative importance of data, to see the whole forest with-

out looking too hard at one tree, which after all is perhaps the most important thing for the practice of good medicine, no matter in what field

In brief, the basic immunologic treatment in many cases of asthma in children is to avoid a very few foods and, insofar as possible, all suspected environmental allergens, and, when indicated, to inject non-specific respiratory vaccines, or in winter, house dust, or in summer, pollens

Any allergic child should be under observation not for weeks or months, but for years. He overcomes some sensitivities, but acquires new ones. He has a constitutional defect, just as a diabetic has, which cannot be changed by any doctor. However, his symptoms can usually be controlled, and he has often—but by no means always—the ability to overcome his sensitivities and cure himself in the course of time. The stage of sensitization in the relations of any young individual with allergenic material is only part of the picture—the most spectacular, to be sure, because he has symptoms during this stage. In order to obtain a complete view of the whole process, his immunologic status after he has passed through the phase of sensitivity needs to be more clearly understood. This tendency to natural acclimatization, development of tolerance, or immunization, if it is permissible to call it so, is perhaps the most striking and important observation that can be drawn from a study of allergy in the young individual. I should like to know better the details of the mechanism by which it is brought about.

# ANALYSIS OF MATERNAL DEATHS AND HOSPITAL OBSTETRICAL STATISTICS IN NEW YORK COUNTY\*

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**T**HE Special Committee on Maternal Welfare of the Medical Society of the County of New York organized a study on Maternal Mortality in May, 1937. This is in reality a continuation of the study of all puerperal deaths in New York City, 1930-1932, by the Committee on Public Health Relations of The New York Academy of Medicine. This study was published in 1933 by The Commonwealth Fund under the title Maternal Mortality in New York City. The analysis group consists of two representatives of each voluntary and municipal hospital in New York County, one of the five counties (Borough of Manhattan) constituting the City of New York.

Meetings are held monthly, and the average attendance varies from eighteen to forty. From ten to fifteen cases are studied at each meeting. These cases are obtained through the cooperation of the Health Department, which gives us copies of death certificates concerned with pregnancy and childbirth. A questionnaire is then sent to the hospital or physician connected with the case. In the very rare instance of a mid-wife attendant, personal contact is made. The Maternity Centre Association has been of great value in the clerical work attached to this study. Since the inception of this work, a total of 171 cases has been studied.

Before presenting an analysis of our cases, it is interesting to study a chart from the Department of Health analyzing the maternal deaths in

\* This report of the Committee on Maternal Welfare of the Medical Society of the County of New York was presented March 28, 1939 before the Section of Obstetrics and Gynecology of The New York Academy of Medicine.

the City of New York for the last four years As may be seen, there has been a progressive decrease in all causes of death The mortality rate per 1000 live births has decreased 33 per cent

New York State has also shown a decrease of 33 per cent The United States has shown a diminution in its maternal mortality rate for the last seven years In 1930 it was 67, and in 1937 it was 488—a diminution of 27 per cent There are only four countries with a higher mortality

The Quarterly Bulletin of the Department of Health of the City of New York in its February 1939 issue makes the following statement

"It is of interest to study the course of the mortality of mothers in childbirth, a problem to which the Advisory Obstetric Council devoted its first attention For many years the maternal death rate had remained almost unchanged Thirty years ago it was 48 per 1000 live births, ten years later it was the same In 1928 it had risen to 53 and by 1933 to 64 Although the maternal mortality rate had fluctuated somewhat in individual years, it would appear that the marked reduction in the rate during the past few years, reflects the excellent work done by the county medical societies in cooperation with the Department of Health "

When one studies Chart I, one may see that puerperal septicemia has decreased by 30 per cent In New York County the reduction is 68 per cent In classification No 148 (Puerperal phlegmasia, alba dolens) are included all cases of puerperal shock and embolus These have diminished but little The difficulty in obtaining autopsies makes it very hard to verify the causes of death Also to be noted is the slight change in the toxemic death rate

#### ANALYSIS OF MATERNAL DEATHS

The 171 cases which we studied occurred during a period of twenty months, from May 1937 to February 1939 We have divided them into four classes, as shown in Chart II

Under the designation, Obstetrical, are included cases in which the most important problem was primarily concerned with childbirth and pregnancy, and not with any other medical or surgical condition Most of the non-puerperal deaths were classified as maternal deaths by the Health Department, which follows the rules promulgated by the Federal Bureau of Census Thus the patients with spinal meningitis and bacterial endocarditis who died undelivered were put in the group of puerperal

CHART I

CITY OF NEW YORK DEATHS FROM PUERPERAL CAUSES,  
BY BOROUGH OF RESIDENCE

1935-1938\*

Int l, 1st N o	Cause of Death	City of New York				Manhattan				Bronx				Brooklyn				Queens				Richmond			
		1935	1936	1937	1938*	1935	1936	1937	1938*	1935	1936	1937	1938*	1935	1936	1937	1938*	1935	1936	1937	1938*	1935	1936	1937	1938*
140	Abortion with septic condition	88	69	61	49—	40	39	31	18—	8	6	5	7+	31	14	14	14+	9	10	10	10+	0	0	1	0—
141	Abortion without mention of sepsis	30	11	12	9—	14	5	0	3+	2	1	2	1—	12	5	7	3—	2	0	2	1—	0	0	1	1+
142	Lectopic Gestation	28	29	33	19—	9	12	10	9—	2	5	8	3—	15	7	12	4—	2	2	3	3+	0	3	0	0+
143	Other accidents of pregnancy	4	3	5	2—	1	1	2	0—	1	0	0	0+	1	1	3	0—	0	1	0	2+	1	0	0	0+
144	Puerperal hemorrhage	74	57	55	63+	27	14	10	16+	11	9	12	6—	20	25	21	19—	15	9	12	14+	1	0	0	8+
145	Puerperal septicemia	86	91	80	61—	25	25	26	8—	10	13	14	13—	40	37	29	26—	8	14	11	13+	3	2	0	1+
146	Puerperal albuminuria and eclampsia	39	46	39	31—	9	10	12	5—	5	13	4	9+	12	16	16	11—	12	6	7	5—	1	1	0	1+
147	Other toxemias of pregnancy	19	14	15	18+	6	3	3	5+	2	3	2	5+	8	6	9	5—	2	2	1	3+	1	0	0	0+
148	Puerperal phlebitis, alba dolens	29	23	18	25+	8	9	3	5+	5	4	3	3+	9	8	10	11+	7	2	1	6+	0	0	1	0—
149	Other accidents of child birth	114	114	86	78—	32	36	12	20+	17	23	23	11—	44	36	34	32—	18	19	16	15—	3	0	1	0—
150	Other conditions of puerperal state	12	2	4	0—	6	1	0	0—	0	0	1	0—	5	1	3	0—	1	0	0	0+	0	0	0	0+
Total puerperal causes		523	459	408	355—	177	155	109	89—	63	77	74	58—	197	156	158	125—	76	65	63	72+	10	6	4	11+
Mortality rate per 1,000 live births		5.2	4.7	4.0	3.5					3.5															

\* Provisional

• Same as 1937

— Decrease in 1938-33%

+ Increase in 1938

## CHART II

## CLASSIFICATION OF 171 MATERNAL DEATHS, BY CAUSE

	Number	Per cent
Obstetrical	104	60.8
Extrauterine	12	7
One full term abdominal pregnancy		
Post abortum	32	18.7
With sepsis	27 or 84 per cent	
Others	5 or 16 per cent	
Non-Puerperal*	23	13.4
Pneumonia	6	
Cardiac	4	
Bacterial Endocarditis	1	
Thyrotoxicosis	1	
Spinal meningitis	1	
Kidney abscess	1	
Acute appendicitis	1	
Chronic nephritis	2	
Ovarian abscess	1	
Miscellaneous	5	

\* Cases where pregnancy and labor had no connection with the death or were contributory with another primary factor

sepsis, because there was an associated fever. On the other hand a cesarean section for premature separation of the placenta in which autopsy showed acute yellow atrophy of liver, was classified as non-maternal. However, conferences were held last year for the purpose of making a new classification of the causes of death, in which contributory factors will be evaluated differently.

Most of the cases of abortion were induced and died of sepsis. However, a case of abortion with pernicious vomiting of pregnancy was classified as an obstetrical death. Under extrauterine pregnancy is included one full term abdominal pregnancy with the placenta left in the abdomen, death was due to the toxemia caused by the absorption of the placenta.

At the meetings of the Mortality Analysis Committee, detailed discussion was principally concerned with the 104 obstetrical deaths analyzed in Charts III to IX. These charts do not analyze the non-puerperal, abortive or ectopic deaths.

## CHAPTER III

CLASSIFICATION OF 104 OBSTETRICAL DEATHS, BY TYPE  
OF HOSPITALIZATION, ATTENDANCE AND PRENATAL CARE*Place of Delivery*

	<i>Number</i>	<i>Per cent</i>
Voluntary hospitals	59	57
Municipal hospitals	22	21
Proprietary hospitals	18	16.3
Home	5	4.7

*Attendants*

Obstetricians and gynecologists	66	63.5
Obstetricians and gynecologists and intern	7	6.7
Obstetricians and gynecologists and general practitioner	5	4.8
General practitioner	9	8.6
Intern	12	11.5
Midwife	2	1.9
General surgeon	1	
Unattended	2	1.9

*Prenatal Care*

Adequate	89	85.6
No care	15	14.4
(Only two of those with no care died of toxemia)		

Fifty-seven per cent of the obstetrical deaths were delivered in the voluntary hospitals. Only 4.7 per cent were delivered at home.

## ATTENDANTS

Sixty-three per cent of the attendants were specialists in obstetrics. Another 11.5 per cent of the patients were attended by interns and general practitioners with the assistance of an obstetrician. There were only two midwife attendants. Thus it can be stated that 75 per cent of the cases received "the best possible skill both in diagnosis and treatment which the community could make available." This is the criterion of The New York Academy of Medicine study in 1933, already cited.

## CHART IV

## CLASSIFICATION OF 104 PUERPERAL DEATHS, BY COLOR

	Number	Percent
White	95	91
Colored	9	9

For the year 1938 in New York County, white births totalled 27,280 or 87 per cent, colored births totalled 3,659 or 13 per cent

## PUERPERAL DEATHS BY COLOR IN 1938—Greater New York City

	Total	White	Colored	Rates (per 10,000 live births)	
				White	Colored
Abortions with sepsis	50	31	19	33	248
Ectopic	19	12	7	13	91
Puerperal hemorrhage	63	57	6	60	78
Puerperal sepsis	61	54	7	57	91
Albuminuria and eclamp	31	27	4	29	52
Other accidents of childbirth	79	73	6	77	78
All other puerperal causes	57	54	3	54	39
<b>TOTAL</b>	<b>357</b>	<b>305</b>	<b>52</b>	<b>823</b>	<b>679</b>

## SOME VITAL STATISTICS FOR THE CENTRAL HARLEM HEALTH CENTER DISTRICT IN COMPARISON WITH RATE FOR NEW YORK CITY

	1934	1935	1936	1937	1938
Maternal mortality rate per 1000 live births	9.2	14.6	17.9	8.5	5.4
New York City	5.9	5.1	4.7	4.0	3.3

## PRENATAL CARE

The question of prenatal care does not seem to be a principal factor, as only 14 per cent lacked adequate prenatal care. This is in accordance with the views expressed by Aranow\* "That while prenatal care is extremely useful in avoiding certain obstetrical complications, its importance in the prevention of maternal mortality has been over-emphasized." However, it must be admitted that no thorough study was made of how adequate that care was.

\* Aranow H. Maternal mortality. *Preventive Medicine* 1937 7 113

## COLOR

Ninety-one per cent of the deaths were of white women and 9 per cent of colored Chart IV (Department of Health) shows the causes of death according to color for the year 1938. The septic abortion death rate in colored women is more than seven times that prevalent in white women and the puerperal sepsis rate almost double. The toxemic death rate is nearly twice that of white. In this respect, New York City parallels the conditions in the Southern States. In Chart IV there is a comparison of the death rates in the Central Harlem Health Center District (which is almost entirely colored) with that of the entire city. The death rate in colored women has dropped almost 50 per cent in five years.

## METHODS OF DELIVERY

Chart V shows the types of delivery and causes of death. More than half of the cases were operative, excluding the breech deliveries, and more than half (55 per cent) of the operative cases were cesarean sections. However, in reference to this question it is well to quote what Israel said in his study of maternal deaths in Erie County:

"Death rates following major operative techniques (version and cesarean section) are definitely higher than those following normal and low forceps deliveries, also, the rates following cesarean sections are definitely higher than those following versions. From the data given no categorical statement can be made that major operative procedures are causes of higher puerperal mortality rates, it can definitely be stated, however, that the two are highly correlated, that greater chance for the mother's death is associated with greater use of such techniques. The real cause of such deaths may be the procedure used, on the other hand, it is equally likely that the complicating conditions which lead to the use of such measures would have caused death in any event. It is probable that the use of these methods has prevented many deaths. The presence of this high degree of correlation between major operative techniques and a high mortality rate complicates rather than simplifies the procedure. In order adequately to determine the relation of such obstetrical methods to the death rate, a statistical study of complicating factors in a large number of unselected cases should be made. Only after such a controlled study, eliminating the effect of such factors, can definite conclusions regarding the importance of such techniques as causes of death per cent,

CHART V

## CAUSES OF DEATH AND METHODS OF DELIVERY OF 104 OBSTETRICAL CASES

Cause of Death	Method of Delivery					
	Spontaneous	Forceps	Cesarean Section	Breath Extraction	Vernier Breech Extraction	Spontaneous Rupture of Uterus
	Number	Per cent	24 Cases	34 Cases	6 Cases	3 Cases
Hemorrhage	35	33.6	12	6	8	1***
Shock	3	2.9	3	—	—	2
Sepsis	24	23.0	7	2	13	—
Pneumonia	6	6.7	1	—	5	—
Loxemia	14	13.4	8	2	2	—
Cardiac	5	4.8	1	1	2	1
Embolus	7	6.7	1	4	1	1
Anesthesia asphyxia	6	5.7	—	4	2	—
Tuberculosis	1	—	—	1	—	—
Infusion reaction	1	—	—	1	—	—
Essential hypertension— Pulmonary edema	—	—	—	—	—	—
	1	—	—	—	—	1
Rupture of bladder, lumbar abscess—embolus	1	—	—	—	—	1
LOAL.	104	—	—	—	—	—

\* From cervical laceration

\*\* Vomitus in lungs in one case

\*\*\* Hemorrhage followed by sepsis

be judged in connection with this question of primacy of delivery methods as causes of death, it is noteworthy that the scheme of classification of death certificates of puerperal deaths given in the Manual of Joint Causes of Death, the official standard of the Census Bureau, gives precedence to the complicating condition for which the operative technique was used, rather than to the operation itself"

Hemorrhage accounts for 33 per cent of the maternal deaths and is thus the principal cause in New York County. This primacy of hemorrhage may be due to the diminution in the sepsis incidence. The wide use of blood transfusion and parenteral administration of fluids has apparently had no influence on the deaths from hemorrhage. There may be a need for a revaluation of the methods used in the treatment of the third stage of labor. Perhaps the amount of hemorrhage is underestimated and more accurate methods to determine the quantity of blood lost should be employed. This whole subject is now being investigated by a special committee appointed by the New York City Board of Health.

In cesarean section, sepsis and pneumonia (the latter may be classified as a septicemia) cause more than half of the deaths in that method of delivery.

Toxemia caused 13.4 per cent of the deaths. Only three were colored, and five had inadequate prenatal care.

Heart disease is an important cause of puerperal deaths. It should be evident that pregnant women with cardiac disease need specialized care.

Anesthesia was a cause of six deaths, four of these during forceps delivery. Our Committee has recommended the employment of well-trained anesthetists in all obstetrical cases.

The case of tuberculosis was noted as an obstetrical death because it was not diagnosed during the early antepartum visits to the prenatal clinic.

#### CAUSES OF DEATH AND METHODS OF DELIVERY IN RELATION TO COMPLICATIONS OF PREGNANCY AND LABOR

Charts VI-IX

(Pages 413-415)

CHART VI  
CESAREAN SECTION

34 Cases or 34.7 per cent of 104 Obstetrical Cases

Classical	13
Low flap	20
Peritoneal exclusion	1

<i>Cause of Death</i>		<i>Complicating Conditions</i>	
Sepsis	13	Prolonged labor	7
Pneumonia	5	Toxemia	4
Hemorrhage	8	Placenta previa	1
Toxemia	2	Cardiac disease	4
Essential hypertension — pulmonary edema	1	Contracted pelvis	3
Embolus	1	Premature separation of the placenta	1
Cardiac failure	2	Primip unengaged head	1
Aspiration asphyxia—anesthesia	2	Elderly primip and fibroids	1
		Elderly primip and fibroids	2
		Bicornuate uterus—transverse presentation	1
		Hemiplegia—essential hypertension	1
		Previous difficult labors	1

CHART VII  
FORCEPS

24 Cases or 23 per cent of 104 Obstetrical Cases

Low	14
Mid	10

<i>Cause of Death</i>		<i>Complicating Conditions</i>	
Anesthesia	4	Prophylactic, or low forceps	9
Hemorrhage	6	Prolonged labor	9
Shock	3	Eclampsia and toxemia	4
Sepsis	2	Low implantation and partial separation of placenta	1
Toxemia	2		
Embolism	4	Cardiac disease	1
Cardiac failure	1		
Rupture of bladder, lumbar abscess, embolus	1		
Transfusion reaction	1		

## CHAPTER VIII

## SPONTANEOUS BIRTHS

31 Cases or 30 per cent of 104 Obstetrical Cases

<i>Cause of Death</i>		<i>Complicating Conditions</i>	
Hemorrhage	12	Antepartum sepsis	2
Sepsis	7	Cardiac disease	1
Toxemia	8	No pathology	7
Embolus	1	Eclampsia and toxemia	10
Pneumonia	1	Retained placenta (2 syphilitic)	1
Cardiac failure	1	Post partum psychosis and pneumonia	
Tuberculosis	1	Low implantation of placenta	1
		Tuberculosis	1
		Diabetes, pyelitis	1

In a consideration of the complicating conditions in operative deliveries, the following facts must be noted

## Cesarean section

(a) In 20 per cent of the cases the indication was prolonged labor. Numerous studies have shown that the danger of a fatality in cesarean section increases with the number of hours the patient has been in labor (including the cases that have had no vaginal examinations)

(b) Twenty of the thirty-four cases of cesarean section were of the low flap type

(c) Only a small proportion of the cases were for contracted pelvis

## Forceps deliveries

More than one-third were prophylactic or low forceps. In this group two of the deaths were due to anesthesia. However, it should be stressed that forceps deliveries per se are not to be considered as the cause of death.

## Breech extraction

Four of these patients died as a result of hemorrhage from a cervical laceration, which was not recognized immediately after delivery.

Edward M. Davis in his address on "Professional Resources and Ability to Provide Good Maternal Care," at the Washington Conference in 1938 states

## CHART IX

## BREECH EXTRACTION

6 Cases or 5.8 per cent of 104 Obstetrical Cases

<i>Cause of Death</i>	<i>Complicating Conditions</i>
Hemorrhage, shock, cervical laceration vomitus in lungs	Twins
Hemorrhage, cervical laceration	Low implantation of placenta
Hemorrhage, cervical laceration	Transverse presentation
Hemorrhage, cervical laceration	Syphilis
Embolus (8th day)	Chronic nephritis, retained placenta (24 hours)
Cardiac death	Mild toxemia

## VERSION AND BREECH EXTRACTION

3 Cases

<i>Cause of Death</i>	<i>Complicating Conditions</i>
Sepsis	Central placenta previa, 5½ months,
Hemorrhage, sepsis, unrecognized cervical laceration	Braxton-Hicks version, incision of cervix
Sepsis	Placenta previa, bag induction, hysterectomy
	Brow presentation, forceps delivery attempted

## SPONTANEOUS RUPTURE OF UTERUS

2 Cases

<i>Cause of Death</i>	<i>Complicating Conditions</i>
Hemorrhage	39 year Para IV, hysterectomy
Hemorrhage	Para V, 31 hours in labor in hospital, hysterectomy

## NOT DELIVERED

4 Cases

<i>Cause of Death</i>	<i>Complicating Conditions</i>
1 Toxemia	Eclampsia
2 Massive accidental hemorrhage	Brought to hospital in shock
3 Toxemia	Pernicious vomiting of pregnancy
4 Found dead at home with rupture of uterus (two previous cesareans)	

"The family practitioner in charge of an obstetric patient may be in need of consultation when complications arise His inability to cope with these complications is no reflection on his training, for in all likelihood he has made the most of these opportunities, but they have not been sufficient to prepare him to meet emergencies"

When one considers the fact that serious obstetric complications occur rather rarely, one can realize the large number of patients the average attendant would have to see in order to develop sufficient skill to treat these complications

E D Plass in an article in the Journal of the American Medical Association (Aug 27, 1938) states

"The struggle to reduce maternal death rates, when viewed in terms of general practice, involves experiences so isolated that their significance may well be lost If a practitioner has fifty obstetric cases annually, he will observe only one serious complication each year and will not have more than one maternal death every four or five years Such isolated experiences are not impressive and are soon forgotten Moreover, their rarity prevents the physician from acquiring the knowledge of diagnosis and treatment essential to saving these occasional patients Under prevailing conditions the wonder is not that so many women die as a result of child bearing, but that so many are carried safely through the perils of procreation"

Before stating our conclusions we present the study which follows of cesarean sections in New York County, prepared by Thomas J Duffield and Sylvia L Parker

In March, 1938, new forms of birth and fetal death (stillbirth) certificates were introduced in the City of New York These new forms included a supplementary confidential medical report, on the back of the certificate, which called for information concerning the period of gestation, weight and length of the infant (fetus) at birth, complications of pregnancy and of labor, mode of delivery, method of induction of labor, if any, etc Mode of delivery had previously been collected with regard to live births but not in connection with stillbirths

For the year 1938, therefore, information regarding mode of delivery is available for 97 per cent of the infants born alive in the County of New York (Borough of Manhattan) Because the old forms of stillbirth certificates did not call for any information on the mode of delivery and because the new forms of fetal death certificates came into use more

slowly than did the new birth certificates, information regarding the mode of delivery of stillborn fetuses was so incomplete during 1938 that the data presented in this paper are based solely on live births, although it is obvious that stillbirths as well as live births figure in both maternal mortality and cesarean sections. At a later date we expect to present data on puerperal mortality and mode of delivery based on the entire recorded exposure to risk.

The total number of live births recorded in Manhattan (New York County) in 1938, the number for which the mode of delivery was stated, and the percentage of infants born alive that were delivered by cesarean section, by color and place of birth, is presented in Chart X. This information is presented for three groups of hospitals—municipal, voluntary and proprietary.

Chart XI shows the variations in individual hospitals in the three classifications, listed in descending order of the percentage of cesarean deliveries among white live births. With the exception of three municipal and two voluntary hospitals, the number of colored births in any individual hospital in the city is so small that the resultant percentages, in general, lack statistical significance.

Regarding the cesarean rates shown in Charts X and XI, it should be pointed out that the decision to use the numbers of total live births rather than the number of live births with mode of delivery stated as the basis for these rates was made in the belief that for the purposes of this paper it was preferable to present cesarean rates which were the minimum values which the actual rates could have, if mode of delivery were known for every birth. That is, it can be stated for each hospital, at least this percentage of the deliveries was by cesarean section. To use percentages based on the numbers for which the mode of delivery was stated would amount to assuming that the cesarean rate among the deliveries with mode not stated was the same as the rate among those with mode stated.

If the proportion of deliveries by unknown mode were greater, or varied much in different groups to be compared, this would of course be a more serious question. As it is, examination of the tables shows that none of the cesarean rates would be changed much, if the rates were based on the number of births for which the mode of delivery was stated. In Table X, for example, the cesarean rates in municipal hospitals would be unchanged, those in voluntary hospitals would be raised from

CHART X

LIVE BIRTHS BY PLACE AND MODE OF DELIVERY  
COUNTY OF NEW YORK (MANHATTAN)

1938

Place of Birth	WHITE			COLORED		
	Live Births		Cesarean Sections	Live Births		Cesarean Sections
	Total	With mode of delivery stated	Number	Total	With mode of delivery stated	Number
5 Municipal Hospitals†	2879	2854	46	16	2681	2665
21 Voluntary Hospitals†	20841	20514	794	38	918	910
11 Proprietary Hospitals†	3016	2889	121	40	17	16
Other Hospitals‡	514	499	16	31	43	39
Total Hospitals	27280	26756	977	36	3659	3630
Home	1528	1169	0	0	680	499
GR AND 101 VI,	28808	27925	977	34	4339	4129
					73	73
						17

† Hospitals with more than 150 live births each in 1938

‡ Hospitals with less than 150 live births each in 1938

\* Number of births too small to allow computation of rate

CHART XI

 CESAREAN SECTIONS IN HOSPITALS HAVING MORE  
 THAN 150 LIVE BIRTHS EACH IN 1938  
 NEW YORK COUNTY (MANHATTAN)

Place of birth	WHITE				COLORED				
	Live births		Cesarean sections		Live births		Cesarean sections		
	Total	With mode of delivery stated	Number	Per cent of total live births	Total	With mode of delivery stated	Number	Per cent of total live births	
<b>5 Municipal Hospitals</b>	<b>Total</b>	<b>2879</b>	<b>2834</b>	<b>46</b>	<b>1 6</b>	<b>2681</b>	<b>2665</b>	<b>31</b>	<b>1 2</b>
A	429	428	9	2 1	94	94	2	2 1	
B	332	330	6	1 8	2213	2200	22	1 0	
C	620	614	10	1 6	162	160	3	1 9	
D	1203	1199	18	1 5	191	190	4	2 1	
E	290	283	3	1 0	21	21	0	*	
<b>24 Voluntary Hospitals</b>	<b>Total</b>	<b>20841</b>	<b>20514</b>	<b>794</b>	<b>3 8</b>	<b>918</b>	<b>910</b>	<b>38</b>	<b>4 1</b>
A	532	527	45	8 5	6	6	1	*	
B	472	469	36	7 6	186	185	6	3 2	
C	974	962	63	6 5	134	133	3	2 2	
D	1624	1614	98	6 0	9	8	0	*	
E	828	814	45	5 4	2	1	0	*	
F	841	839	38	4 5	1	1	0	*	
G	537	534	24	4 5	31	31	0	0 0	
H	2157	2154	92	4 3	315	315	19	6 0	
I	586	565	24	4 1	2	2	0	*	
J	459	446	19	4 1	7	7	0	*	
K	1020	1013	41	4 0	0	0	0	*	
L	1062	1055	40	3 8	26	25	2	*	
M	314	311	11	3 5	17	17	0	*	
N	428	415	14	3 3	1	1	0	*	
O	2781	2781	85	3 1	112	112	5	4 5	
P	392	379	12	3 1	17	17	0	*	
Q	464	422	13	2 8	1	0	0	*	
R	815	814	22	2 7	20	20	2	*	
S	552	533	14	2 5	1	1	0	*	
T	876	839	19	2 2	7	6	0	*	
U	1097	1014	19	1 7	19	18	0	*	
V	814	808	12	1 5	1	1	0	*	
W	954	950	7	0 7	0	0	0	*	
X	262	256	1	0 4	3	3	0	*	
<b>11 Proprietary Hospitals</b>	<b>Total</b>	<b>3046</b>	<b>2889</b>	<b>121</b>	<b>4 0</b>	<b>17</b>	<b>16</b>	<b>1</b>	<b>*</b>
A	241	240	19	7 9	0	0	0	*	
B	362	334	27	7 5	1	1	1	*	
C	232	232	13	5 6	2	2	0	*	
D	596	515	28	4 7	0	0	0	*	
E	399	382	16	4 0	0	0	0	*	
F	144	142	5	3 5	6	6	0	*	
G	189	189	6	3 2	2	1	0	*	
H	234	225	5	2 1	0	0	0	*	
I	169	159	1	0 6	2	2	0	*	
J	315	307	1	0 3	2	2	0	*	
K	165	164	0	0 0	2	2	0	*	

\* Number of births too small to allow computation of rate

## CHART XII

## NEW YORK COUNTY (MANHATTAN) MATERNAL MORTALITY\*

1938

Place of Birth	WHITE			COLORED		
	Live births	Number of deaths*	Rate per 1000 live births	Live births	Number of deaths	Rate per 1000 live births
5 Municipal Hospitals†	2679	17	5.9	2661	8	3.0
24 Voluntary Hospitals†	20841	38	1.8	918	4	4.4**
11 Proprietary Hospitals†	3046	10	3.3	17	0	0.0**
Other Hospitals‡	514	3	5.8**	13	0	0.0**
Total Hospitals	27280	68	2.5	3659	12	3.3
Home	1528	2	1.3**	680	0	0.0**
GRAND TOTAL	28808	70	2.4	4339	12	2.8

\* Puerperal Mortality, exclusive of deaths associated with abortion or ectopic gestation

\*\* Based on too small numbers for rates to have statistical significance

† Hospitals with more than 150 live births each

‡ Hospitals with less than 150 live births each

3.8 and 4.1 to 3.9 and 4.2, respectively. The largest change would be in the white rate in proprietary hospitals, which would be raised from 4.0 to 4.2. In Chart XI, the greatest changes would be in the white rates for proprietary hospitals B and D where the rates would become 8.1 and 5.4, respectively, instead of 7.5 and 4.7. Conclusions drawn from these cesarean rates were subjected to the most stringent test possible, that is, examining whether the conclusion would still hold if, while keeping the *higher* of two cesarean rates at its minimum possible value, the *lower* of the two rates were given its maximum value by assuming that all the deliveries of unknown mode in that group were cesareans.

The five municipal hospitals as a group reported cesarean deliveries of 1.6 per cent of the infants born alive to white mothers and 1.2 per cent to colored mothers. In the voluntary hospitals the percentages among white and colored were 3.8 and 4.1, respectively. These figures indicate that cesarean section is much more frequently practiced in the

voluntary than in the municipal hospitals. This comparison holds even under the stringent test described above. That is, assuming that in municipal hospitals every one of the 25 live births to white mothers for which the mode of delivery was not stated was a cesarean delivery, there would have been 71 cesarean sections, giving a rate of 25 per 100 live births. This figure is still considerably below the rate of 38 per 100 live births in voluntary hospitals, though the rate of 38 in voluntary hospitals treats the 327 live births for which the mode of delivery was not stated as if none of them was a cesarean. The corresponding test of the cesarean rate for colored mothers, assuming every one of the 16 unknowns in municipal hospitals to have been a cesarean, would make 47 cesareans, giving a rate of 18 per 100 live births, in comparison with the minimum rate of +1 in voluntary hospitals.

For any particular type of hospital the cesarean rates were not significantly different for white and for colored mothers. For all white mothers, on the other hand, the cesarean rate, 34 per cent, was twice as high as that for all colored mothers, 17 per cent. This is an apparent contradiction to the previous statement. It is easily explained, however, by the fact that 65 per cent of the *colored* live births in Manhattan occurred in the municipal hospitals where the cesarean rate was low, whereas only 10 per cent of the *white* live births occurred in the municipal hospitals.

Detailed study of the maternal mortality records for the individual hospitals does not show any relationship between the percentage of cesarean sections performed and the mortality experienced. The figures are not included in Chart XI as the numbers are too small to justify any computation of rates. Chart XII gives, however, the mortality figures for groups of hospitals. It is to be noted that in the municipal hospitals which obtain a larger proportion of their cases as emergency admissions through ambulance calls, the maternal mortality among white mothers was higher than in either the voluntary or the proprietary hospitals. This is in agreement with other statistics available where a distinction is made between patients receiving adequate prenatal care and those admitted as emergencies. The higher maternal death rate in municipal hospitals occurs in spite of the very much lower cesarean rate in those institutions. The maternal mortality rate for colored mothers, however, was not higher in municipal hospitals than in voluntary hospitals.

As a final conclusion to be drawn from the above tables, it should

be emphasized that when abortions and ectopics are excluded, the maternal mortality rate for white mothers was only 24 per 1,000 live births and that for colored mothers was 28 per 1,000 live births

### CONCLUSIONS

1) It has been said that the great progress in the practice of medicine was a result of a thorough study of autopsy material and discussion of cases at regular clinical pathological conferences. The latter term can be applied to the work of our Maternal Mortality Study Group. It can easily be seen how great is the educational value resulting from a study of maternal deaths among 30,000 annual births, which are discussed from the different viewpoints of the representatives of twenty-five hospitals, and four medical colleges.

2) When one considers that about 90 per cent of obstetrical cases will be delivered without any difficulty, and that the complications and obstetrical emergencies occur so rarely, one can readily see how difficult it is to acquire the art of obstetrics. In addition, the facilities for the teaching of the student, the intern as well as the specialist, are very limited. Perhaps the answer to this problem may be compulsory consultations in all difficult obstetrical cases. This policy has already been advocated by a number of medical societies (Kings County and Philadelphia) and has received practical support from the Federal Government.

3) It is apparent from our analysis of hospital deliveries that the cesarean rate is high in some institutions. It is also true that more than one-third of the obstetrical deaths occur in cesarean section. However, the municipal hospitals, with the lowest cesarean rate, have a higher mortality rate than the voluntary and proprietary hospitals. This is probably due to the fact, that the municipal hospitals have a much larger number of ambulance emergency patients, who usually have a greater number of obstetrical complications. Perhaps there is also an economic factor, with its associated malnutrition and poor physical condition present in the municipal hospital cases.\* It has been stated that obstetrics is passing through a transition stage and that with the standardization of procedures and indications for operation, this operative mortality will be still further reduced. Towards this latter end it must be evident that the work of our Mortality Analysis Group should be a great help.

We have not discussed the question of preventability of the maternal deaths. The numerous studies published on that subject in the last few

years have already produced their full value in exciting an interest in the subject of maternal mortality. However, in any popularization of the figures of preventability there should be a separation of the deaths resulting from abortion and extrauterine pregnancy, from those associated with the difficulties of childbirth and labor.

At our meetings for the analysis of cases, we discuss and vote on preventability. The question of preventability is very often difficult to decide. We feel that the greatest value to be obtained from our analysis, is that of learning from the unfortunate results before us.

\* In discussing James K. Quigley's paper on "Maternal Welfare: What Are Its Fruits?" (*Am J Obst & Gyn* 1940 **39** 349), the following statement was made by a Dr. James R. McCord:

"There is probably more in the problem of maternal mortality than good obstetric care. You can take any map of maternal mortality rates and you find that most of the Southern States have high rates. Also, in general, the colored rates are nearly twice as high as the whites. You might immediately say that we are not doing good obstetric work in the South."

I live in a city of approximately one half million people with a colored population of 150,000. We deliver about 2,200 colored women a year in our clinic in the municipal hospital. Our obstetric service is far from being a finished service but it is a conservative service. Our total operative incidence is 3.96 per cent which includes the packing of the vagina. Our forceps incidence for term and premature deliveries is 1.3 per cent. The cesarean incidence 0.46 per cent and yet we have an uncorrected maternal mortality rate of 6.4 per 1,000 pregnancies. These women are getting good obstetric care and yet we have a tremendous mortality rate. Approximately 45 per cent of the women on our service are either illegitimately pregnant, the husband unemployed or on W.P.A.

With agriculture in the depths negroes all over the South are moving into the larger communities where they are badly housed and ill fed. Sepsis is the killer of colored women and certainly on our service we can conscientiously say that it is in large measure not our fault. I do not mean in the least to deprecate good obstetric care but I do believe that permanent lowering of maternal mortality must be accompanied by a proportionately rising economic level.

## RECENT ACCESSIONS TO THE LIBRARY

'Possession does not imply approval'

Association for Research in Nervous and Mental Disease *The hypothalamus and central levels of autonomic function*  
Balt, Williams, 1940, 980 p

Bing, R *Compendium of regional diagnosis in lesions of the brain and spinal cord*  
11 ed  
St Louis, Mosby, 1940, 292 p

Bodansky, M & Bodansky, O *Biochemistry of disease*  
N Y Macmillan, 1940, 684 p

Burdon, K L *A textbook of microbiology*  
2 ed  
N Y, Macmillan, 1939, 638 p

*Contribution to radiology in honor of Dr I Seth Hirsch by his pupils and friends, 1939*  
[Syracuse, Radiological Society of North America, 1940], 402 p

Crofton, W M *The true nature of viruses*  
2 ed  
London, Bale, [1940-], 166 p

Cushing, H W *The medical career, and other papers*  
Boston, Little, 1940, 302 p

Duval, J F *La gastrectomie, operation banique* 2 ed  
Paris, Maloine, 1939, 107 p

Harrower, H R *An endocrine handbook*  
Glendale, Cal., Harrower Laboratory, 1939, 127 p

Janeson, E M & Sewell, M *Trends in nursing history*  
Phil, Saunders, 1940, 570 p

McCall, J O & Wald, S S *Clinical dental roentgenology*  
Phil, Saunders, 1940, 319 p

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St Louis, Mosby, 1940, 671 p

Mobley, H E *Synopsis of operative surgery*  
St Louis, Mosby, 1940, 375 p

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Oliver, O A, Irish, R E & Wood, C R *Labio-lingual technic a description of the labial and lingual appliances in the treatment of malocclusion*  
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Balt, Williams, 1940, 175 p

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Sansoni, W D, Koehler, A L & Bowden, R *A manual for diabetic patients*  
N Y, Macmillan, 1939, 227 p

Selling, L S *Men against madness*  
N Y, Greenberg, [1940], 342 p

Stephani, J *Études radiographiques du poumon tuberculeux*  
Paris, Fert, 1939, 138 p

Stroninger, I *Les erreurs et les fautes en urologie*  
Paris, Masson, 1939, 176 p

Thomen, A S A *Doctors don't believe it Why should you?*  
N Y, Regent Press, 1940, 350 p

Uslenghi, J P, Hofmann, H & Hedpern, M J *La fotografía del estomago*  
Buenos Aires, Lopez, 1939, 215 p

Younans, J B *Essentials of the diagnostic examination*  
N Y, Commonwealth Fund, 1940, 417 p

Ziegler, P F *Textbook on sutures*  
Walpole, Mass., Lewis Mfg Co, [1939], 70 p

## PROCEEDINGS OF ACADEMY MEETINGS

### S I F F D M E E T I N G S

**April 4**—*The New York Academy of Medicine* Executive session—*a*] Reading of the minutes, *b*] Vote on amendments to constitution and by-laws & The Fifteenth Herman Michael Biggs Memorial Lecture, "Heart disease—a world problem," Paul Dudley White, Lecturer in Medicine, Harvard Medical School, Physician, Massachusetts General Hospital & Report on election of members

**April 18**—*The Harvey Society in affiliation with The New York Academy of Medicine* The Seventh Harvey Lecture, "Morphologic and Functional Alterations of the Coronary Circulation," Joseph I. Weitz, Professor of Medicine, Western Reserve University School of Medicine

### S E C T I O N M E E T I N G S

**April 2**—*Section of Dermatology and Syphilology* Presentation of cases—*a*] City Hospital, *b*] New York Polyclinic Hospital, *c*] New York Hospital and Cornell Medical College *d*] Miscellaneous cases & General discussion & Executive session Nomination of Section Officers and one member of Advisory Committee

**April 5**—*Section of Surgery* Reading of the minutes & Presentation of cases—*a*] A case of bilateral paralysis of inferior laryngeal nerve following thyroidectomy with spontaneous recovery, Henry F. Graham (by invitation) Discussion, William C. White *b*] Parathyroid adenoma—multiple bone cyst formation, pathological fracture, cure following operation, Irwin E. Siris, Discussion, William Bradley Parsons *c*] Curettage of the thyroid (2 cases) Frank B. Berry Discussion, Howard A. Patterson, *d*] A case of hyperparathyroidism, Norman L. Higinbotham Discussion, Bradley

*e*] Coley & Papers of the evening—*a*] Cancer of the thyroid, William I. Wilson, John Pool, Discussion, Frederic Bancroft, Arthur S. McQuillin *b*] Recurrences in hyperthyroidism, Edwin B. Eckerson, Discussion, Morris K. Smith, *c*] The treatment of postoperative tetany, Francis M. Donchue, Discussion, Otto Pickhardt & General discussion & Executive session Nomination of Section Officers and one member of Advisory Committee

**April 9**—*Section of Neurology and Psychiatry* Reading of the minutes & Presentation of cases—*a*] A case of thromboangiitis obliterans with cerebral involvement, D. J. Impastato (by invitation) *b*] Postencephalitic palsies and pallesthesia and forced singing (from the New York University Neuro-psychiatric Division of Welfare Hospital), S. Bernard Wortis, Martin H. Stein (by invitation), Sidney Govoni (by invitation) & Papers of the evening—*a*] Neuro-spongiosis of the skin and pathological aspects, Joseph H. Globus Discussion, Otto Marburg (by invitation), Lewis D. Stevenson, *b*] Further experience with cervical rib and the scoliosis inferior syndrome, Russell Patterson Discussion, Bronson R. IV & Executive session Nomination of Section Officers and one member of Advisory Committee

**April 11**—*Section of Pediatrics* Executive session—*a*] Reading of minutes *b*] Nomination of Section Officers and one member of Advisory Committee & Papers of the evening—*a*] Tachycardia in the new born, Herman Einhorn (by invitation) Discussion Burton Littin *b*] Relationship of the jaws from birth to three years of age J. H. Sillman D.D.S. (by invitation) Discussion Harry Bakwin *c*] The use of sulfamethizol in severe staphylococcal infections, Donald Weisman (by invitation) Discussion, Harry Nelson

(by invitation), d] Bacteriological and epidemiological distinctions between Grade A and Grade B pasteurized milk in New York City, Haven Emerson, representing the staff of the DeLamar Institute of Public Health of the College of Physicians and Surgeons, Columbia University ¶ General discussion

APRIL 15—*Section of Ophthalmology* Instruction hour—Neuro-ophthalmology, Kaufman Schliek, Demonstration of slit lamp cases—Gordon M Bruce, Girolamo Bonaceolto, Milton Berliner ¶ Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶ Presentation of cases—a] Subacute dacryadenitis with fusiform bacillus conjunctivitis, Webb P Chamberlain (by invitation), b] Plastic material for orbital implantation, Conrad Berens, Sidney Rothbard (by invitation), c] Autokeratoplasty, Wendell L Hughes, Discussion, John C Cunningham (by invitation), d] A simple suture for retention of corneal graft, Sigmund A Agatston ¶ Papers of the evening—a] Observations on the innervation and pharmacology of the eye muscles, Morris Bender (by invitation), b] Retrobulbar neuritis an analysis of one hundred cases, Frank D Carroll ¶ General discussion

APRIL 16—*Section of Medicine* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶ Papers of the evening—a] Histamine in anaphylaxis and allergy, Laurence Farmer, b] Histaminase Physiologic effects on man and its therapeutic value in medicine, Grace M Roth, PhD, Mayo Clinic (by invitation), Bayard T Horton, Mayo Clinic (by invitation), Discussion, David Perla ¶ General discussion

APRIL 17—*Section of Genito-Urinary Surgery* Executive session—a] Reading of minutes, b] Nomination of Section Officers and one member of Advisory Com-

mittee For Chairman, John H Morrissey, For Secretary, Frank C Hamm, For Member of Advisory Committee, Simon A Beisler, c] Election of Section Officers and one member of Advisory Committee ¶ Papers of the evening—a] A simplified method of nephropexy (motion picture), John Dust Discussion, O S Lowsley, b] The genesis, diagnosis and treatment of urinary tuberculosis, Oscar Auerbach, Sea View Hospital (by invitation), William P Herbst, Georgetown Medical School (by invitation), John L Emmett, Mayo Clinic (by invitation) ¶ Discussion

APRIL 17—*Section of Otolaryngology* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶ Papers of the evening—a] Sphenoiditic hydrocephalus, Irving B Goldman, Discussion, George A Blakeslee, b] Pontofacial angle tumors with particular reference to involvement of the acoustic nerve, Joseph H Globus, Discussion, Byron Stookey, c] Localized non-suppurative encephalitis of otorhinologic origin, Miles Atkinson (by invitation), Discussion, Emanuel D Friedman, James G Dwyer ¶ General discussion

APRIL 19—*Section of Orthopedic Surgery* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶ Papers of the evening—a] Fascial transplants for abdominal paralysis, Nicholas Ransohoff, Discussion, Leo Mayer, b] Two-stage transplantation of the fibula for infected pseudarthrosis and congenital pseudarthrosis of the tibia, Philip Wilson, Discussion, John J Nutt, c] Osteoid osteoma, Henry L Jaffe, Discussion, A Sumner Prieur ¶ General discussion

APRIL 23—*Section of Obstetrics and Gynecology* Executive session—a] Reading of the minutes, b] Nomination of Section Officers and one member of Advisory Committee ¶ Papers of the evening—a] The mental hygiene of preg-

nancy, labor and the puerperium, Margaret E Fries, Discussion, Claude E Heaton, Lawrence S Kubie, b] Causes of death in carcinoma of the cervix uteri, an analysis of 124 autopsies in 1558 cases, Lionel S Auster, Angelo M Sala, c] The hormonal etiology of cervical carcinoma, Anthony Wollner

#### AFFILIATED SOCIETIES

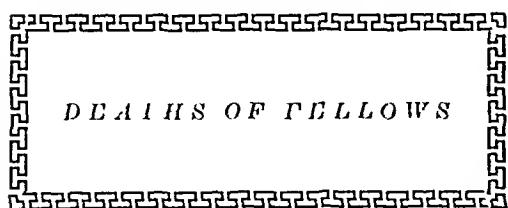
MARCH 18—*New York Roentgen Society* (in affiliation with *The New York Academy of Medicine*) Presentation of cases  
 §§ Papers of the evening—a] The shrunken pulmonary lobe, Oswald R Jones (by invitation), b] The vanishing lung, Stanton T Allison (by invitation) §§ Discussion §§ Executive session

MARCH 28—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*) Case reports—a] Hemangioendothelioma of lung, Alfred Plaut, b] An unusual case of congenital heart disease, M W Johannsen §§ Papers of the evening—a] A consideration of so-called "granulosa" and "Theca" cell tumors of the ovary, Herbert F Fraut, b] Host-parasite relationships in some virus encephalitides, Lester S King

APRIL 15—*New York Roentgen Society* (in affiliation with *The New York Academy of Medicine*) Presentation of cases  
 ♦ Papers of the evening—1] A simpli-

fied operation for Meniere's syndrome and for intractable pain in the distribution of the glosso pharyngeal and the trigeminal nerves, Abraham Kaplan (by invitation), b] An x-ray aid in the diagnosis of acute polyphlebitis (portal thrombosis), Anthony Bissler (by invitation), c] Case of pelvic actinomycosis treated by surgery and Roentgen ray, Harriet C McIntosh, Maurice Rishbaum (by invitation), d] Motion picture Roentgen kymographic studies of the movements of the small intestine and colon, George A Weltz, Munich, Germany (by courtesy of Wendell G Scott, St Louis) ♦ Discussion, Foster Kennedy (by invitation), Maurice Rishbaum (by invitation) ♦ Executive session

APRIL 25—*New York Pathological Society* (in affiliation with *The New York Academy of Medicine*) Case reports—a] Iorula infection of the central nervous system, Leo Wiede (by invitation), b] Human tissue response to an unidentified microorganism resembling the bacillus lignieresii and past (pseudo-glanders), F J Curphey ♦ Papers of the evening—1] Evaluation of postmortem bacteriology, Caspar G Burn, b] Intracranial pathways for the extension of infection from the sphenoo-ethmoid sinuses, Rudolph Kramer (by invitation), Max L Som (by invitation) ♦ Executive session



## DEATHS OF FELLOWS

COE, HENRY CLARKE Clifton Terrace, Washington, D. C., born in Cincinnati, Ohio, February 21, 1856, died in Washington, D. C., April 21, 1940, received the degrees of A. B. in 1878 and M. A. in 1881 from Yale University, M. D. from Harvard University Medical School in 1881 and from the College of Physicians and Surgeons, Columbia University, in 1882 M. R. C. S. (England) 1884, and L. R. C. P. (London) 1884, elected a Fellow of the Academy January 15, 1885

Dr. Coe was emeritus professor of gynecology at New York University College of Medicine and at one time consulting gynecologist to the Bellevue, Women's, Polyclinic, Beth Israel, St. Joseph's, Southside and Memorial Hospitals. He was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association and a member of the State and County Medical Societies.

During the World War, Dr. Coe served two years in foreign service as Colonel of the Medical Corps of the U. S. Army and was cited for distinguished service.

KRAETZER, ARTHUR FURMAN 123 East 53 Street, New York City born in Brooklyn, April 16, 1891, died in New York City, March 4, 1940 graduated in medicine from Cornell University Medical College in 1916, elected a Fellow of the Academy February 3, 1927

Dr. Kraetzer was director of medicine at the Knickerbocker Hospital, associate attending physician to the Lenox Hill Hospital and attending physician to the thyroid out-patient-department at that institution. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

RIGGS, AUSTIN FOX Stockbridge, Massachusetts, born in Cassel, Germany, December 12, 1876, died in Stockbridge, March 5, 1940, received the degree of A. B. from Harvard University in 1898, M. D. from the College of Physicians and Surgeons, Columbia University, in 1902, and Sc. D. from Williams College in 1937, elected a Fellow of the Academy December 7, 1905

Dr. Riggs was founder, medical director and president of the Austin Riggs Foundation, clinical professor of neurology at the College of Physicians and Surgeons, Columbia University, consulting psychiatrist to Vassar College (Poughkeepsie) and William's College (Williamstown), and consulting neurologist to the House of Mercy Hospital at Pittsfield.

During the World War, Dr. Riggs recruited and commanded the American Relief Corps Ambulance No. 13 and after this country's entrance he served as a member of the Medical Advisory Board of the first and second selective military drafts. He was a lieutenant in the Medical Reserve Corps of the United States Army at his death.

Dr. Riggs was a diplomate of the American Board of Psychiatry and Neurology, a Fellow and life member of the American College of Physicians, a Fellow of the American Medical Association, a member of the American Neurological Association, the American Psychiatric Association, the National Committee on Mental Hygiene, and the Massachusetts and New York State Medical Societies.

Dr. Riggs was the author of "Just Nerves," "Intelligent Living," and "Play."

ROBERTS, DUDLEY DE VORE 420 Lexington Avenue, New York City, born in Newark, New Jersey, March 1, 1874, died in New York City, March 9, 1940, graduated in Medicine from the College of Physicians and Surgeons, Columbia University, in 1898, elected a Fellow of the Academy January 2, 1919.

Dr. Roberts was consulting physician to the United States Marine Hospital at Stapleton, Staten Island, and a member of the American Gastro-Enterological Association.

THE NEW YORK ACADEMY OF MEDICINE  
EXTENDS A CORDIAL WELCOME TO THE  
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AT NEW YORK CITY